SUPPORTED PROGRESSIVE RESISTANCE TRAINING FOR COUNTERING THE ADVERSE SIDE EFFECTS OF PROSTATE CANCER TREATMENT

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SUPPORTED PROGRESSIVE RESISTANCE TRAINING FOR COUNTERING THE ADVERSE SIDE EFFECTS OF PROSTATE CANCER TREATMENT

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“However difficult life may seem, there is always something you can do and succeed at. It matters that you don’t just give up”

Professor Stephen Hawking 1942-2018

Abstract

Exercise is recommended for cancer patients due to its positive effects on treatment side effects and quality of life. Currently no structured exercise guidelines for prostate cancer patients exist and most advice is aimed at those receiving androgen deprivation therapy (ADT). The over-arching aim of this thesis is to develop an exercise programme to improve cardiometabolic health in patients treated for prostate cancer, particularly via robot-assisted radical prostatectomy, and assess its effectiveness through a randomised controlled trial.

Resistance exercise training has shown via a systematic review and meta-analysis, to be effective for inducing improvements in resting blood pressure, endothelial function, blood biomarkers and aerobic capacity and is a safe mode of exercise in both healthy and clinical populations (Chapter 3). This thesis also demonstrates that some men after robot-assisted radical prostatectomy are at increased risk of cardiovascular disease within ten years of surgery and suffer with clinically significant levels of fatigue (Chapter 4). Furthermore men after robot-assisted radical prostatectomy appear to meet the Government recommended guidelines for aerobic physical activity but not for resistance-based exercise.

Patient and public involvement was integral to this thesis with the patients leading on the design and implementation of the exercise programme (Chapter 5). The results of the randomised controlled trial (Chapter 6), demonstrated that resistance exercise training had a clear effect on body composition, aerobic capacity, strength, functional wellbeing and prostate cancer specific quality of life and showed evidence of a favourable reductions in resting blood pressure and some blood biomarkers.

Collectively, this thesis provides evidence that resistance exercise training is effective in improving multiple cardiometabolic health benefits in men who have undergone robot-assisted radical prostatectomy whilst being a safe and well-received mode of exercise. Therefore, resistance exercise training can generally be considered a useful adjunct therapy for this patient population.

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List of Abbreviations

ACSM – American College of Sports Medicine

ANCOVA – Analysis of Covariance

BFI – Brief Fatigue Inventory

CABG – Coronary Artery Bypass Graft

CPET - Cardio-Pulmonary Exercise Test

CRP – C-Reactive Protein

CVD – Cardiovascular Disease

DBP – Diastolic Blood pressure

DNA – Deoxyribose Nucleic Acid

DRE – Digital Rectal Examination

DXA – Dual X-ray Absorptiometry

ECG – Echocardiogram

FMD – Flow-Mediated Dilatation

FMDr - Flow-Mediated Dilatation with Respect to Recovery Diameter

GnRH - Gonadotrophin Releasing Hormone

GP – General Practitioner

GLUT-4 Glucose Transporter Type 4

HDL-chol – High-Density Lipoprotein Cholesterol

HOMA-IR – Homeostatic Model Assessment of Insulin Resistance

HRQOL – Health-related Quality of Life

IGF-1 - Insulin-Like Growth Factor-1

IL-6 – Interleukin-6

ISRCTN - International Standard Random Controlled Trials Number

LDL-chol – Low-Density Lipoprotein Cholesterol

LHRH - Luteinizing Hormone Releasing Hormone

MAP – Mean Arterial Pressure

METs – Metabolic Equivalent Task Hours

MP-MRI – Multi-Parametric Magnetic Resonance Imaging

MRC – Medical Research Council

MRI – Magnetic Resonance Imaging

MVPA – Moderate to Vigorous Physical Activity

NHS – National Health Service

NICE - National Institute of Health and Care Excellence

NUTH – Newcastle Upon Tyne Hospitals NHS Foundation Trust

PPI – Patient and Public Involvement

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSA – Prostate Specific Antigen

PTCA - Percutaneous Transluminal Coronary Angioplasty

RCTs – Randomised Controlled Trials

RET – Resistance Exercise Training

RPE – Rating of Perceived Exertion

SBP – Systolic Blood Pressure

SMD – Standardised Mean Difference

SPAQ – Scottish Physical Activity Questionnaire

TNM – Tumour Node Metastasis

TRUS – Transrectal Ultrasound

VEGF - Vascular Endothelial Growth Factor

$\dot{V}O_2$Peak – Peak Rate of Oxygen Consumption

Publications and Conference Proceedings Arising from this Thesis

Publications

Ashton, R.E., Tew, G.A., Aning, J.J., Gilbert, S.E., Lewis, L., & Saxton, J.M. (2018). Effects of short-, medium- and long-term resistance exercise training on cardiometabolic health outcomes in adults: systematic review and meta-analysis. British Journal of Sports Medicine. doi: 10.1136/bjsports-2017-098970. [Epub ahead of print]

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Conference Proceedings

Ashton, R.E., Tew, G.A., Saxton, J.M., Robson, W. & Aning, J.J. "Prospective pilot study of patient-reported fatigue, physical activity and cardiovascular status in men after robotic-assisted radical prostatectomy". Proceedings of The British Association of Urological Surgeons, Liverpool, UK, 52-27th June 2018.

Ashton, R.E., Tew, G.A., Saxton, J.M., Robson, W. & Aning, J.J. "Supported progressive home-based resistance training for improving fitness and physical functioning post robot-assisted radical prostatectomy: preliminary findings". Proceedings of The Royal Society of Medicine Urological Day Academic Meeting, London, UK, 23rd April 2018.

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To my immediate family, thank you for not only providing support, patience and encouragement but also maintaining an appearance of interest in my work over the last three and a half years.

Finally, I wish to dedicate this PhD thesis to my Dad, who himself was treated for prostate cancer in 2011 and is here to celebrate the handing in of this thesis.

Declaration

I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas and contributions from the work of others.

Any ethical clearance from the research presented in this thesis has been approved. Study approval was obtained on (ref: 202404) from the Health Research Authority (Appendix 1a). Ethical approval from NHS REC South Scotland was obtained on 8th September 2016 (ref: 16/SS/0143; Appendix 1b) and approved by NUTH Research and Development on 11th October 2016 (ref: 7832; Appendix 1c).

I declare that the word count of this thesis is 37,947.

Name: Ruth Ashton

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Date:

CHAPTER 1

GENERAL INTRODUCTION

1.0 General Introduction

The physiology of exercise is the study of how the body responds and adapts to exercise. The benefits of both acute and chronic exercise have been studied extensively in numerous populations. In recent years, exercise research has become more prevalent, with a focus on improving the outcomes of inactive populations and the effectiveness of varying exercise interventions in patient's with chronic diseases.

It is essential for exercise programmes to be individualised taking each person's needs, abilities and health issues into consideration (Brown et al., 2011; F. Campbell et al., 2015; Hardcastle et al., 2018; Vashistha, Singh, Kaur, Prokop, & Kaushik, 2016). Therefore, it is important to identify the most suitable exercise programmes for different populations, particularly those with chronic diseases. Clinical populations may benefit most from structured exercise programmes in addition to usual care due to the positive effects they can have on the illness, treatment side effects and patient quality of life.

Exercise has been recommended for patients being treated for cancer (Meneses-Echavez, Gonzalez-Jimenez, & Ramirez-Velez, 2015; National Institute for Health and Care Excellence, 2014b). Cancer is a disease characterised by uncontrolled or abnormal cell proliferation. Prostate cancer is the most common malignancy in men aged 40-65 years and usually develops slowly with prostate cancer risk increasing with age, abdominal obesity and family history (Gann, 2002; Heidenreich et al., 2011) and the majority of cases being diagnosed in men over the age of 65 years (Smittenaar, Petersen, Stewart, & Moitt, 2016). Exercise is recommended for men being treated for prostate cancer by both the National Institute for Health and Care Excellence (NICE) and the American College of Sports Medicine (ACSM). This is due to the positive effects it can have on on physical and mental health, as well as its potential role in reducing disease progression and reoccurrence after treatment (Chodzko-Zajko, 2009; National Institute for Health and Care Excellence, 2013; Riebe, Ehrman, Liguori, Magal, & American College of Sports Medicine, 2017). However, there are currently no structured exercise

guidelines for prostate cancer patients and most advice is aimed at those who have received androgen deprivation therapy (ADT).

Prostate cancer treatment, either through robot-assisted radical prostatectomy or ADT, carries numerous side effects, including urinary incontinence, negative mental state and erectile dysfunction (Lardas et al., 2017; Lehto, Tenhola, Taari, & Aromaa, 2017). The side effects of ADT are well documented and include increases in body fat, unfavourable changes in blood borne biomarkers of cardiometabolic health (e.g. high cholesterol levels, insulin resistance) and reduced bone mineral density (Bourke et al., 2011; Keilani et al., 2017). Robot-assisted radical prostatectomy on the other hand often results in erectile dysfunction and urinary incontinence, alongside increased body mass, reduced skeletal mass and impaired physical functioning, potentially leading to unfavourable blood borne biomarkers of cardiometabolic health (Adam et al., 2017; Barocas et al., 2017; Joshu et al., 2011; Keilani et al., 2017; Santa Mina, Alibhai, et al., 2013). All the side effects of both treatments can consequently negatively impact a patient's physical function and quality of life (Keilani et al., 2017; Keogh & MacLeod, 2012; Santa Mina et al., 2010; Smith et al., 2001).

The effect of resistance exercise training (RET) on cardiovascular and metabolic health outcomes remains unclear. However, some studies have reported favourable improvements in body composition, blood glucose, fasting insulin and lipid profile as well as increases in muscle strength and aerobic capacity in healthy elderly adults and type 2 diabetes patients (De Salles, 2010; Nikseresht, Agha-Alinejad, Azarbayjani, & Ebrahim, 2014; Romero-Arenas et al., 2013; Sañudo et al., 2013; Sigal et al., 2007). In addition, RET may help to attenuate the age and treatment related loss of muscle mass often observed in men treated for prostate cancer through robot-assisted radical prostatectomy or ADT (Chodzko-Zajko, 2009; Keogh & MacLeod, 2012). Such benefits could improve health-related quality of life, reduce fatigue and improve overall physical functioning. The optimal RET programme for maintaining skeletal muscle mass and cardiometabolic health in prostate cancer patients is unknown and there is a need for more research. Given the treatment-

associated health issues that prostate cancer patients face, it seems worthwhile to investigate how a RET programme, developed to maintain or enhance skeletal muscle mass and cardiometabolic health, might be incorporated into the patient care pathway to reduce treatment side effects and likelihood of developing cardiometabolic comorbidities (World Health Organisation, 2017).

Chapter 2 provides an overview of the risk factors, pathophysiology and diagnosis of prostate cancer, the effect of treatments on cardiometabolic health and quality of life and how exercise could be incorporated into the pathway of care to attenuate the treatment side effects. Chapters 3 comprises a systematic review and meta-analysis of the effects of RET on cardiometabolic health outcomes in adults. Chapter 4 describes a survey of prostate cancer patients regarding their daily exercise levels and fatigue. Chapter 5 outlines the development of a RET programme to maintain or enhance skeletal muscle mass and cardiometabolic health in prostate cancer patients receiving robot-assisted radical prostatectomy and ADT. Chapter 6 reports a clinical trial in which the primary aim was to investigate the effects of the RET programme on indices of cardiometabolic health in a group of robot-assisted radical prostatectomy patients. Chapter 7 includes a general discussion, consideration of research limitations and overall conclusions.

CHAPTER 2

LITERATURE REVIEW

2.0 Literature Review

2.1 The Prostate Anatomy

The prostate is located within the male pelvis and forms part of the male reproductive system (Figure 1). The function of the prostate is to secrete an alkaline fluid which contributes to the ejaculate. The base of the prostate is directly below the bladder neck, the gland surrounds the urethra. The seminal vesicles, which also contribute fluid towards the ejaculate, are attached to the base of the prostate next to the bladder.

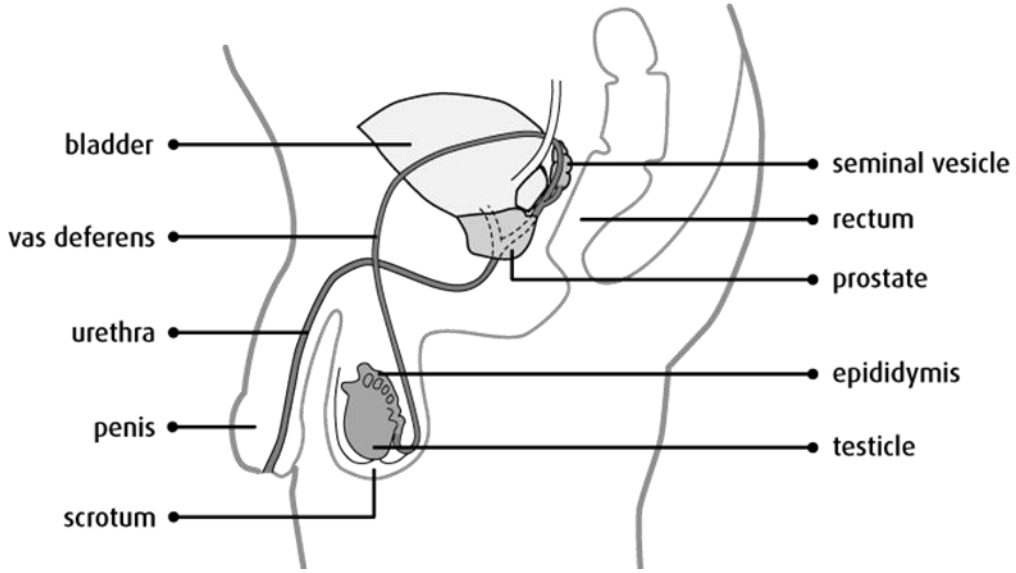

Figure 1. Location of the prostate in relation to other organs (Canadian Cancer Society, 2018).

2.2 Pathophysiology of Prostate Cancer

Prostate cancer is the most common malignancy in men aged 40-65 years and is often slow growing and, due to the location of the prostate, often affects urination (Cancer Research UK, 2015). The majority of prostate cancers are classified as an adenocarcinoma, being most common in the peripheral zone of the prostate. Over time, cancer cells multiply in an unregulated fashion to form a tumour that has the potential to invade nearby organs such as the

seminal vesicles or rectum, or the tumour cells may develop the ability to travel in the blood stream and lymphatic system – a condition referred to as metastasis.

The majority of prostate cancers are initially highly dependent on androgens for growth. Androgens are naturally occurring hormones that regulate the development and maintenance of male characteristics. The activation of androgen receptors involves several co-regulators (proteins that interact with transcription factors) that respond to a changing microenvironment to regulate specific gene targets involved in cell growth and survival. In a normal prostate epithelium, there is a balance between the rate of cell proliferation and the rate of apoptosis, however, in prostate cancer this process is unbalanced, leading to tumour growth.

All cells, including prostate cells, require a level of programming, known as epigenetics, to maintain their function, regenerate, and divide normally. Epigenetics involves heritable changes in gene function and expression, without changes to the base sequence of deoxyribose nucleic acid (DNA). These changes are influenced by environmental factors, such as diet (Choi, 2010), smoking (Kanherkar, Bhatia-Dey, & Csoka, 2014) and physical activity (F. F. Zhang et al., 2011), and can exert significant influence on an individual's phenotype via increased DNA methylation or decreased acetylation of associated histones. Such changes in the genes can cause cells to mutate and rapidly divide leading to cancer. Methylation is a normal and important part of development and transcription regulation however epigenetic dysregulation is associated with the development of cancer. Hypomethylation of DNA is common in cervical, prostate, stomach, lung, bladder, oesophageal, colorectal, breast and liver cancers in various cell and tumour types (Jin, Li, & Robertson, 2011; Lu et al., 2006). In addition, hypermethylation of tumour suppressor genes can be altered with ageing and also promote oncogenesis, and is well established in many common human cancers (e.g. prostate cancer) (Lu et al., 2006; Massie, Mills, & Lynch, 2017). Such genetic mutations in a given cancer can be reasonably heterogeneous between individuals, yet there are multiple epigenetic mutations that appear to be common in particular cancers, including

prostate cancer (Yegnasubramanian, 2016). Recently glutathione S-transferase-π (GSTP1) methylation has been detected in many types of cancer and has a prevalence of > 90% in prostate cancer (Henrique & Jeronimo, 2004). As GSTP1 methylation has been detected in circulating DNA, it could be a promising future biomarker of prostate cancer detection and reoccurrence (Benedettini, Nguyen, & Loda, 2008; Henrique & Jeronimo, 2004).

2.3 Prostate Cancer Prevalence and Incidence

Cancer tends to be a disease of ageing with approximately a third (36%) of all cancer cases in the United Kingdom being diagnosed in patients 75 years and older each year. In 2015, more than half of all new cancers cases in the UK were either breast, prostate, lung or bowel cancer and the number of males diagnosed with cancer across the majority of sites in 2014 and 2015 was consistently higher than females (Cancer Research UK, 2017; Office Of National Statistics, 2017).

Worldwide, more than 1.11 million men were estimated to have been diagnosed with prostate cancer in 2012, with the incidence varying across the world. Prostate cancer is a condition that, in the early stages, often does not present any symptoms (Heidenreich et al., 2011; Ngollo et al., 2014) and its incidence is increasing with 299,923 (corresponding to 822 per day) new cases being registered in England in 2015; an increase of 3060 from the same time point in 2014 (Office Of National Statistics, 2017). There is also some evidence of an association between prostate cancer incidence and deprivation in England. Prostate cancer is one of the few cancers where incidence rates, despite rising overall, are lower for males living in more deprived areas (Cancer Research UK, 2017). An ageing population, improved health awareness and screening for prostate cancer using the prostate specific androgen (PSA) blood test are thought to account for the increasing incidence of the disease in higher socioeconomic classes (Cancer Research UK, 2016; Siegel, Miller, & Jemal, 2017). The prevalence of prostate cancer in the UK is estimated to rise to 29% by 2035 which could be, at least partially, attributable to further

advances in screening and awareness of the disease (Cancer Research UK, 2015; Smittenaar et al., 2016).

2.4 Prostate Cancer Risk Factors

Prostate cancer is linked to multiple non-modifiable risk factors such as family history of prostate cancer, age and ethnicity as well as modifiable risk factors including diet, physical activity and, overweight and obesity.

The risk of being diagnosed with prostate cancer increases with age but with increasing age many patients also suffer from other comorbidities (Farmer, 2008; Ng et al., 2017). The aetiology of prostate cancer is unknown, however, in the majority of cases, prostate cancer will have been present for a long indolent period suggesting that many prostate cancers are the result of genetic damage over a sustained period (Bostwick et al., 2004; Gann, 2002). Age-specific incidence curves show that the number of new prostate cancer cases begins to rise sharply at 55 years of age and peaks at 75-79 years of age (Cancer Research UK, 2016; Gann, 2002). After 80 years of age there is a slight decline in prostate cancer diagnoses before a subsequent steady increase to over 90 years of age (Cancer Research UK, 2016).

The inheritance of prostate cancer has been investigated in numerous ways, including case-control studies, cross-sectional studies, family studies and studies of twins, providing consistent evidence to support a level of genetic susceptibility. The risk of prostate cancer is increased by approximately 2-3-fold if an individual has a first-degree relative (i.e. brother or father) with a history of prostate cancer (Gann, 2002; Heidenreich et al., 2011). Risk is further increased if prostate cancer is diagnosed at an early age in a relative or an individual has multiple relatives with the disease and, this risk appears to be constant across different ethnic groups (Farmer, 2008; Heidenreich et al., 2011). It has been estimated that gene alterations could explain approximately 10% of all prostate cancer cases, however it is not yet known the number of genes involved or the specific sequence changes in these genes (Gann, 2002; Lecarpentier et al., 2017).

Ethnicity is recognised as a risk factor for the development of prostate cancer disease. Several studies have noted higher incidence rates for prostate cancer among African-American men, who have a higher risk of prostate cancer than white men and also have a worse prognosis (Bostwick et al., 2004; Farmer, 2008; Gann, 2002; Kheirandish & Chinegwundoh, 2011). It is thought that race-related discrepancies in prostate cancer risk may, in part, be due to factors including dietary differences, genetic mutations as well as differences in the detection of the disease and access to healthcare (Bostwick et al., 2004; Kheirandish & Chinegwundoh, 2011).

Alongside non-modifiable risk factors there are some modifiable lifestyle factors that can potentially reduce the risk of prostate cancer development. Diet is associated with some types of cancer and, given that it can vary between social and ethnic groups, it is unsurprising that the effect of diet on prostate cancer has been investigated recently. It has been suggested that high amounts of animal fats in the diet, obesity (particularly abdominal obesity) and vitamin D deficiency can increase the risk of prostate cancer (Farmer, 2008; Hori, Butler, & McLoughlin, 2011; Labbé et al., 2014; Mandair, Rossi, Pericleous, Whyand, & Caplin, 2014). These factors are thought to account for approximately 10% of the difference in incidence between black and white men (Farmer, 2008). Despite much research into the effects of diet on prostate cancer development, there remains no conclusive result. It does, however, remain a plausible risk factor as diet, excess weight and their related alterations in endogenous hormones such as androgens, insulin-like growth factor I (IGF-I), insulin and leptin, can result in an internal environment for prostate cancer to develop (Kaaks et al., 2003). Excess fat mass is known to reduce sex hormone–binding globulin levels, potentially leading to an increase in bioavailable testosterone, insulin and bioavailable IGF-1, which are possibly important in prostate cancer growth (Gann, 2002; Gill, Wilkens, Pollak, Stanczyk, & Kolonel, 2010; Kaaks et al., 2003). However there appears to be a lack of consistency amongst studies regarding the association between physiological levels of plasma androgens and prostate cancer risk. Such controversies exist despite strong indirect evidence of their tumour-stimulating

effects however, this may be due to the complex associations between androgens and IGF-I, insulin and leptin.

In addition to diet, it has also been suggested that physical activity can, not only reduce body fat but also could potentially reduce prostate cancer risk, particularly the risk of being diagnosed with high-grade disease (Cosimo et al., 2016; Friedenreich & Thune, 2001; Moore et al., 2009). Physical activity has previously been described as “any bodily movement produced by skeletal muscles that results in energy expenditure… that can be categorized into occupational, sports, conditioning, household, or other activities” (Caspersen, Powell, & Christenson, 1985, p. 126). With walking accounting for the majority of physical activity undertaken, it has previously been reported that men diagnosed with prostate cancer who engaged in ≥ 90 minutes of walking a week had a 61% (95% CI, 0.18 to 0.84) lower risk of prostate cancer mortality when compared to men who walked for much shorter durations (Kenfield, Stampfer, Giovannucci, & Chan, 2011; Richman et al., 2011). Exercise differs from physical activity in that it is “planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness” (Caspersen et al., 1985). Few studies have investigated the amount of exercise and its direct relationship with prostate cancer risk. However, findings from one study suggest that a moderate amount of structured exercise (3-8.9 metabolic equivalent task hours (METs) a week) may lead to a reduced risk of prostate cancer diagnosis, and in men with prostate cancer it may be associated with a lower risk of high grade disease (Antonelli et al., 2009; Cosimo et al., 2016). Further to exercise reducing the risk of prostate cancer, exercise post diagnosis can reduce overall prostate cancer mortality and improve quality of life therefore, exercise advice may become an important component of the treatment pathway for prostate cancer (Bourke et al., 2014; Kenfield et al., 2011; Lynch & Leitzmann, 2017), and especially as CVD is the leading cause of death among men with prostate cancer (Allott, Masko, & Freedland, 2013). However, more research is needed in the form of randomised controlled trials, to understand the benefits of

different exercise modes on prostate cancer risk and the effectiveness of exercise as part of the treatment pathway.

2.5 Economic Burden of Prostate Cancer

Driven by an increased incidence and prevalence, partly influenced by ageing populations, improved survival and improved care that has made cancer a chronic, controllable illness, cancer now accounts for an ever increasing proportion of global spending on healthcare (Bosanquet & Sikora, 2004). In 2009, the UK spent approximately £12.8 billion on cancer related health care with prostate cancer initial treatment costs on average totalling £3300 per patient (Fourcade et al., 2010; Luengo-Fernandez, Leal, Gray, & Sullivan, 2013). The total per patient costs are highly dependent upon cancer stage at diagnosis, survival and choice of treatment and, despite declining prostate cancer mortality rates, costs are expected to rise due to improved diagnosis, diagnosis at an earlier stage and increased survival, therefore increasing the economic burden (Cancer Research UK, 2015; Fourcade et al., 2010; Roehrborn & Black, 2011). Robot-assisted radical prostatectomy is a common method of treatment for patients with localised prostate cancer (see section 2.8) rather than open surgery and a recent study has demonstrated that, although more costly in the first instance, it is more effective in maintaining function, reduced surgical margins and results in a reduced hospital length of stay (Close et al., 2013; Finkelstein et al., 2010). Cancer care results in medical, morbidity and mortality costs to the NHS and therefore the economic planning of cancer services in the UK requires detailed consideration.

2.6 Detection and Diagnosis

There is no national screening programme in place for prostate cancer. The vast majority of men will have no symptoms, however, prostate cancer can cause haematuria (blood in the urine), erectile dysfunction and urinary symptoms (Wilt & Thompson, 2006). To relieve some of the existing burden

on the health system and reduce invasive procedures on otherwise healthy men, a more effective way of diagnosing prostate cancer is needed. A major concern in the detection of prostate cancer is the need to differentiate between indolent and aggressive diseases to prevent over-diagnosis and over-treatment of inactive or slow growing disease and to allow aggressive treatments to be suitably allocated (Massie et al., 2017). Currently, the main methods to diagnose prostate cancer include serum concentration of PSA followed by digital rectal examination (DRE), magnetic resonance imaging (MRI), and transrectal ultrasound (TRUS)–guided biopsies.

2.6.1 NICE Pathway of Care

Often men initially present to a General Practitioner (GP) with symptoms associated with prostate cancer (e.g. urinary frequency, haematuria, discomfort during urination) and/or undergo a PSA blood test whilst with the GP (J. Aning, 2018). If it is suspected that a man has possible prostate cancer, they are referred to local urology services for in-depth assessment. All men are offered individualised information in the form of leaflets, websites and support groups by a consultant or specialist nurse. The results of the PSA, DRE, comorbidities and family history are then used to inform prostate biopsy. The decision of undergoing a prostate biopsy is with the patient once the consultant or specialist nurse has provided all relevant information and support. There are two main types of prostate biopsy; (1) TRUS-guided and, (2) template (transperineal) biopsy. Biopsies are not usually offered to men if the suspicion of prostate cancer is high either due to high PSA and evidence of bone metastases unless it is a requirement of a clinical trial. Once all diagnostic tests are complete, specialists use the staging system described in section 2.7 (page 17) to inform the most appropriate treatment pathway for each individual. Figure 2 shows the NICE pathway of care for a male with suspected prostate cancer (National Institute for Health and Care Excellence, 2014b).

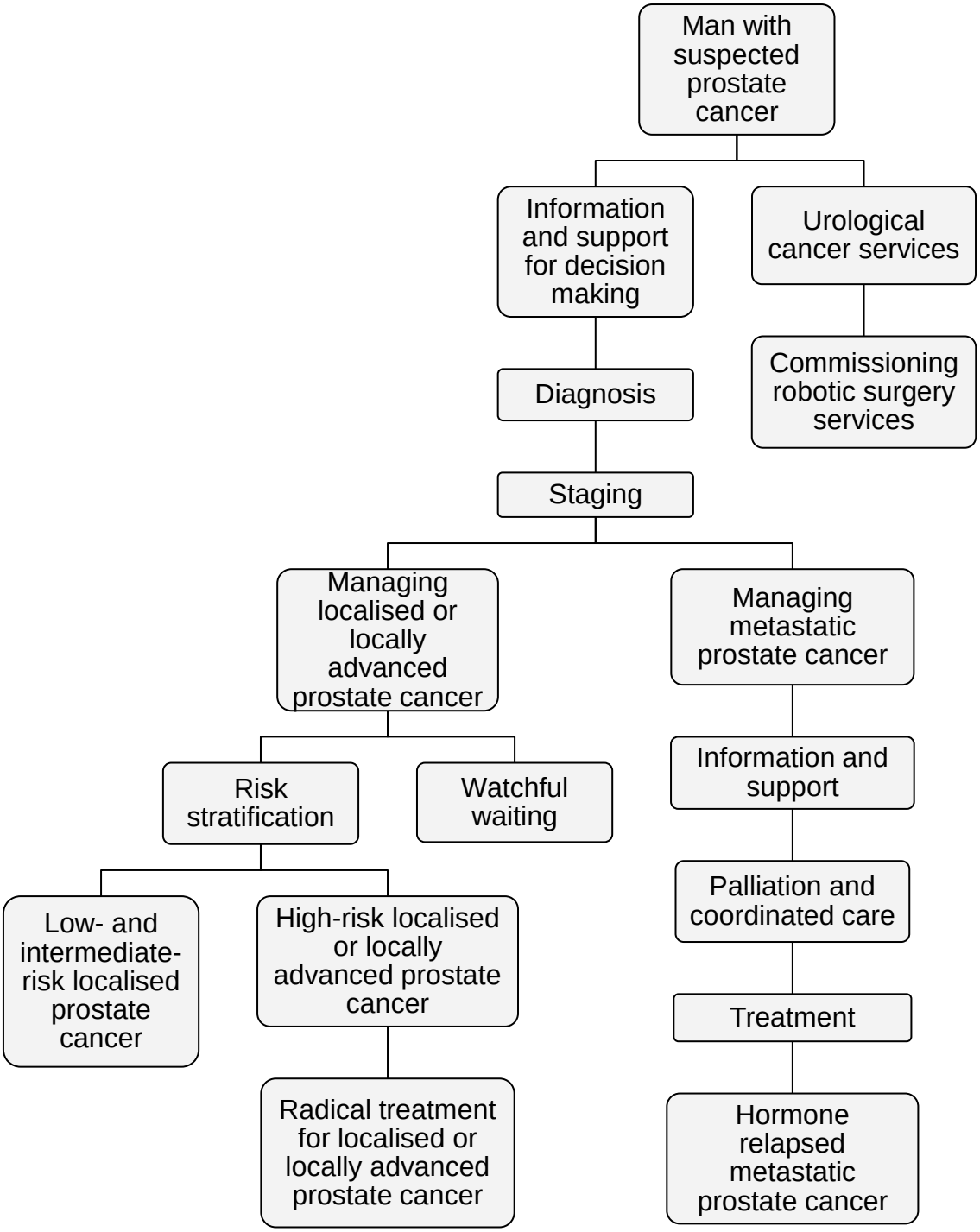

Figure 2. Pathway of care for those suspected with prostate cancer. Adapted from NICE 2014 (National Institute for Health and Care Excellence, 2014b).

2.6.2 Prostate Specific Androgen

PSA is a protein made in the prostate which can be measured in the blood of men (produced by prostate epithelial cells) and is currently used to aid prostate cancer diagnosis. Raised PSA concentrations may be associated with prostate cancer but also enlargement and inflammation of the prostate gland (Wilt & Thompson, 2006). PSA testing has increased over recent years, however, there is some controversy that surrounds the sensitivity and specificity of PSA testing (Kim & Andriole, 2015; Yegnasubramanian, 2016). Testing of PSA levels is often initiated by either the patient or physician and a PSA ≥ 3 ng/ml has been used as a biomarker to guide further investigation or biopsy (Aus et al., 2005; J. L. Donovan et al., 2018). However, there is concern that PSA testing is of limited benefit to men > 70 years of age or those with limited life expectancy (Wilt, Scardino, Carlsson, & Basch, 2014). The poor specificity of PSA testing can potentially lead to unnecessary prostate biopsies being carried out. It has therefore been recommended that biopsies should not be taken immediately after the initial PSA test, but rather the PSA test should be verified by a second test a few weeks later under the same conditions, except for initial tests that return high PSA values (> 20 ng/ml; (Heidenreich et al., 2008)).

2.6.3 Digital Rectal Examination

During a DRE, a clinical physician palpates the prostate through the rectum with their finger. DRE accuracy can be highly user dependent (Wilt & Ahmed, 2013). The majority of prostate cancers are located peripherally and so may be detected during a DRE, however a substantial proportion may either be organ confined or in the anterior prostate and thus not palpable at DRE. DRE also confers the opportunity to estimate the size of the prostate which may also be a causative factor for an elevated age specific PSA (European Association of Urology, 2016).

2.6.4 Biopsies

A high PSA level and/or a suspicious DRE, as well as the patient's age and potential comorbidities, are determinants for biopsies. TRUS-guided biopsy is the most common method of histopathological confirmation of suspected prostate cancer. The procedure involves passing an ultrasound probe into the rectum to image the prostate in real time and enabling the passage of a fine needle alongside the ultrasound probe to penetrate the prostate gland to retrieve biopsy samples. TRUS-guided biopsies are undertaken without prior knowledge of the area of the prostate in which the cancer could be located and therefore often leads to the over diagnosis of low-risk prostate cancer and the under-diagnosis of clinically important cancers (Ahmed et al., 2017; Grönberg et al.). Transperineal (template) prostate biopsy differ from TRUS-guided biopsies in that the needle samples the prostate through the perineum rather than the rectum. The procedure is carried out under either general or local anaesthetic and, using a grid template with holes 5 mm apart, the needle is inserted into each hole to sample the entire prostate gland. In the case of persistently increasing PSA values or an abnormal DRE, repeated biopsies may be performed (Heidenreich et al., 2011).

The use of MRI over recent years has shifted from a staging tool to being used for detection and location purposes in prostate cancer patients (Figure 3). Due to the high soft-tissue contrast and image resolution, MRI is one of the best imaging tools available to clinicians allowing image-guided prostate biopsies, therefore overcoming the limitations of blind prostate sampling, avoiding unnecessary TRUS-guided biopsies and improving diagnostic accuracy (Ahmed et al., 2017; Futterer et al., 2015). Multiparametric-MRI (MP-MRI) is different to traditional MRI in that it combines up to three different types of scan and a contrast agent is injected to enhance the image produced. Multiparametric-MRI possess considerably better sensitivity and predictive value for clinically important prostate cancer when compared with TRUS-guided biopsies and could be used as a triage test prior to biopsy, thereby decreasing unnecessary biopsies and over detection of clinically insignificant disease (Ahmed et al., 2017; Thompson et al., 2014).

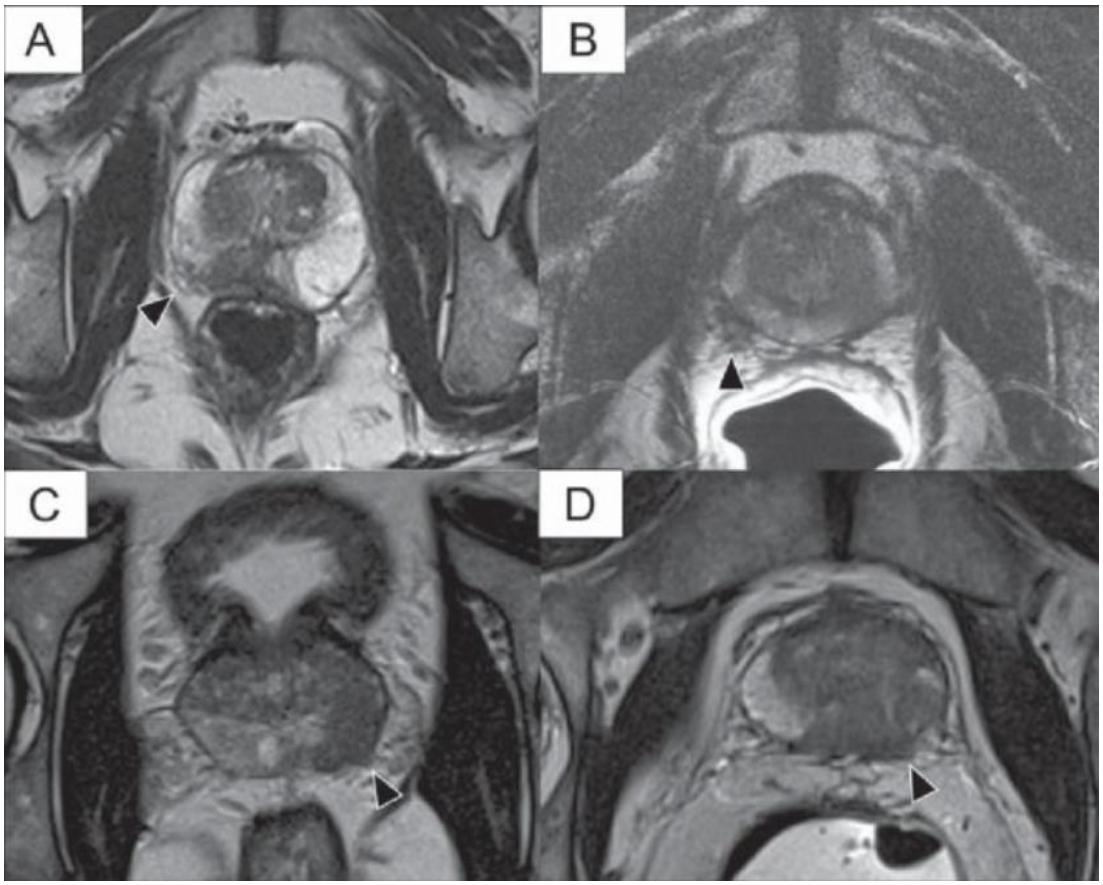

Figure 3. MRI scan of a prostate with arrowheads marking extracapsular cancerous tumour extension (Bittencourt, Hausmann, Sabaneeff, Leandro Gasparetto, & Barentsz, 2014).

2.7 Classification of Prostate Cancer

Classifications of prostate cancer describe the extent and severity of the disease and are important when deciding on a patient's treatment plan. The current histologic prostate cancer grading system was developed between 1966 and 1974 by Donald Gleason and the Veterans Administration Cooperative Urologic Research Group (Gleason, 1992) and has since been the single most powerful predictor of prostate cancer risk. Since the original Gleason grading system, diagnosis and treatment has evolved leading to modifications to the grading system. Epstein *et al.* (Epstein et al., 2016) described the histologic definitions of the five grade groups in the new grading

system (Table 1). Currently, the Gleason grade classification is combined with the tumour-node-metastasis (TNM) staging system (Table 2) to provide a comprehensive definition of a patient's disease.

Table 1. Gleason grading system.

Grade	Score	Description
1	Gleason score 3 + 3 = 6	Only individual discrete well-formed glands
2	Gleason score 3 + 4 = 7	Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands
3	Gleason score 4 + 3 = 7	Predominantly poorly formed/ fused/cribriform glands with lesser component of well-formed glands
4	Gleason score 8	Only poorly formed/fused/cribriform glands. Predominantly well-formed glands and lesser component lacking glands. Predominantly lacking glands and lesser component of well-formed glands
5	Gleason scores 9–10	Lack of gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

Table 2. Tumour-node-metastasis staging system for prostate cancer. Adapted from the American Joint Committee on Cancer (Cancer, 2003).

Localised Disease	**T categories – size and spread of the tumour**	
	TX: Primary tumour cannot be assessed **T0:** No evidence of primary tumour	
	T1: Cancer is within the prostate. It cannot be detected during a DRE and there are generally no symptoms	**T1a:** Tumour in 5% or less of tissue resected
		T1b: Tumour in more than 5% of tissue resected
		T1c: Tumour identified by biopsy
	T2: Cancer is confined to the prostate but is large enough to be felt during a DRE or apparent on a scan	**T2a:** Cancer is only in one half of one of the two lobes of the prostate gland
		T2b: Cancer is in more than one half of one of the lobes of the prostate
		T2c: Cancer is in both lobes
Locally Advanced	**T3:** Cancer has spread outside of the prostate	**T3a:** Cancer is not affecting the surrounding structures
		T3b: Cancer has spread into seminal vesicles
	T4: Tumour is fixed or has invaded adjacent structures other than seminal vesicles	
Lymph Nodes	**N categories – spread of cancer to local lymph nodes**	
	NX: Nearby lymph nodes were not assessed	
	N0: No regional lymph node metastasis	
	N1: Metastasis in regional lymph nodes	
Metastatic Disease	**M Categories – spread of the cancer to other body parts**	
	M0: No distant metastasis	
	M1: Distant metastasis	**M1a:** Cancer has spread to distant lymph nodes
		M1b: Cancer has spread to the bones
		M1c: Cancer has spread to other organs with or without spread to the bones

2.8 Treatment Options, Aims and Side Effects

It is not possible to state that one therapy is superior over another when considering treatment for prostate cancer. This is due to numerous factors such as the patient characteristics and the stage of the disease and therefore treatment is individualised to each patients needs. However, the management of prostate cancer looks to reduce disease-specific and all-cause mortality and, prostate cancer progression whilst maintaining patient quality of life and improving prostate cancer cure rate (J. J. Aning, Wassersug, & Goldenberg, 2012; Jayadevappa et al., 2017; Johnson, 2016). The treatment options considered for prostate cancer are detailed below.

2.8.1 Active Surveillance

Active surveillance, sometimes called active monitoring, is the recommended treatment option for monitoring prostate cancer that is low-risk and localised to the prostate. It involves regular monitoring of the disease through PSA and DRE checks approximately every 3-6 months. Active surveillance is offered to men who: (1) have localised prostate cancer and radiotherapy or robot-assisted radical prostatectomy are suitable and the future risk has been assessed as low, or (2) have localised prostate cancer and the future risk has been assessed as intermediate and the patient does not wish to have active treatment straight away (National Institute for Health and Care Excellence, 2014b). If there is concern about clinical or PSA changes at any time during active surveillance patients are usually reassessed with MP-MRI and/or re-biopsy. The patient can elect to have curative active treatment at any time during active surveillance. The disadvantages of this treatment strategy include: (1) potentially having more biopsies can be uncomfortable, (2) over time, health may change, and the cancer could grow meaning some treatments would no longer be viable, and (3) the cancer may grow faster than expected and be more difficult to treat.

2.8.2 Watchful Waiting

Watchful waiting is a method of monitoring prostate cancer that is not causing any symptoms or problems for the patient with the aim of monitoring it over the long term, and avoid treatment unless symptoms arise. Watchful waiting is often recommended to older men when it is unlikely that the cancer will shorten the life span or they possess other health problems in which active treatment would be deemed inappropriate (Mottet N.). In those who chose watchful waiting, PSA is measured once a year usually at a GP surgery rather than a hospital. If there are any signs that the cancer is progressing, the patient may be referred back to a hospital for further tests to be conducted. If the disease has progressed, treatment is usually given to relieve symptoms and improve quality of life rather than be curative.

2.8.3 Radical Prostatectomy

Robot-assisted radical prostatectomy involves surgical removal of the prostate and is now, in the majority of cases, the most common method of prostate removal (National Institute for Health and Care Excellence, 2014b). Performing the robot-assisted radical prostatectomy rather than open surgery in the treatment of prostate cancer often improves surgical margins and reduces blood loss, pain and results in a faster recovery time for patients (Tewari et al., 2012). However robot-assisted surgery may not be suitable for all patients who have localised prostate cancer or locally advanced prostate cancer if they possess other conditions, such as decreased cardiopulmonary reserve, vascular disease or are morbidly obese, which increase the risk of complications of major surgery (Maerz, Beck, Sim, & Gainsburg, 2017; Mottet et al., 2019). Patients are discharged from hospital approximately 1-3 days post laparoscopic surgery with a catheter that usually remains in place for 2 days to two weeks. However, patients can expect to not attend work for a minimum of 8-12 weeks post-treatment. The side effects surgery include erectile dysfunction, urinary incontinence, potential muscle wastage and increased fat mass in the 8-12 weeks post-surgery and cancer related fatigue.

2.8.4 Radiotherapy and Brachytherapy

Two types of radiotherapy are used for the treatment of prostate cancer; external and internal - with the type dependent on various factors such as the size, grade and stage of cancer. External beam radiotherapy involves radiation being targeted at the prostate cancer from a linear accelerator. External radiotherapy can also be used to shrink secondary tumours that have spread to bones and are causing pain. Internal radiotherapy, commonly known as brachytherapy, involves inserting small radioactive implants into or next to the cancerous tumour or placing radioactive seeds into the prostate (National Institute for Health and Care Excellence, 2014b). External beam radiotherapy uses beams (X-ray or gamma rays) of high-energy radiation focused on cancerous tissue and may be used as an alternative to surgery (National Institute for Health and Care Excellence, 2015). The aim of radiotherapy is to cure cancer when provided in cases of localised disease but to control the growth of the disease in cases of advanced disease. The side effects of radiotherapy and brachytherapy are for example, bowel and urinary problems, erectile dysfunction and cancer-related fatigue.

2.8.5 Androgen Deprivation Therapy

ADT refers to treatments that act by reducing the effects of testosterone and other androgens, thus inhibiting the growth and progression of prostate cancer and is available to men with localised, locally advanced and advanced prostate cancer (National Institute for Health and Care Excellence, 2014b). ADT is used to control the progression of cancer and can be achieved by either suppressing the secretion of testicular androgens or by inhibiting the action of androgens circulating in the body (Mottet et al., 2019). Luteinizing hormone-releasing hormone (LHRH) agonists are the most common type of injection or implant and include medications such as Zoladex® and Prostap®. Gonadotrophin releasing hormone (GnRH) antagonists are found in the drug degarelix (Firmagon®) for the treatment of prostate cancer that has spread to the bones, and as such, are used less often than LHRH agonists. Both LHRH and GnRH

work by supressing the release of testicular androgens. Conversely there are tablets that can be taken to block the effects of testosterone (anti-androgens) such as bicalutamide (Mottet et al., 2019). These two methods can also be combined to achieve what is known as maximal androgen blockade. Erectile dysfunction, unfavourable changes to body composition, reduction in bone mineral density and cancer-related fatigue are all side effects of ADT.

2.8.6 Chemotherapy

Chemotherapy is not a common treatment for prostate cancer however it is used for more advanced cases (i.e. metastatic prostate cancer). Chemotherapy utilises cytotoxic medicines to interrupt how the cells divide and multiply, therefore killing or stopping the growth of the cancer. Usually, chemotherapy drugs need to enter the bloodstream to travel to all areas of the body to reach the cancerous cells. The most common chemotherapy drug is docetaxel and side effects of this treatment include: (1) hair loss, (2) cancer-related fatigue, (3) nausea and vomiting, and (4) bowel problems.

2.9 Effect of Exercise Training on the Side Effects of Treatment

The side effects of the multiple prostate cancer treatments are greatly diverse, therefore, in keeping with the focus of this PhD, only studies with relevance to patients who have been treated via robot-assisted radical prostatectomy or ADT will be discussed further. This section will discuss the impact of prostate cancer treatment on physical function and quality of life.

2.9.1 Impact of Treatment on Physical Function

In addition to the risk of CVD, ageing males suffer from a reduction in the levels of circulating testosterone, resulting in muscle atrophy, decreased sexual desire, viable sperm and prostate disorders, with prostate cancer treatments

accelerating and exacerbating some of these problems. Additionally, both surgical and ADT treatments for prostate cancer can result changes to body composition. Patients tend to be sedentary in the 8-12 weeks post-surgery, therefore potentially resulting in an increase in fat mass and a decrease in muscle mass and strength, but the extent of this is yet to be investigated. On the other hand, ADT results in female pattern weight gain (for example increased fat mass and a reduced muscle mass) due to the hormonal changes induced to reduce the progression of prostate cancer (Galvao et al., 2006; Higano, 2003; Keilani et al., 2017). Those on ADT are reported to have approximately 24% less muscular strength, 7% less aerobic capacity, and 20-27% less functional performance ability in repeated chair rise and walking tests (Galvao et al., 2009; Henwood & Taaffe, 2006; Keogh & MacLeod, 2012). Such changes can result in an increased risk of insulin resistance, fatigue and falls, particularly in older individuals (Fiuza-Luces et al., 2018; Walston, 2012). Furthermore, these changes can impact on self-confidence and result in premature fatigue and prevent patients from carrying out work and normal activities of daily living (Keogh & MacLeod, 2012; Storer, Miciek, & Travison, 2012). If fatigue becomes persistent, it may prevent prostate cancer patients from engaging in physical activity and can lead to detrimental changes in blood pressure, blood lipid profile and other changes that are indicative of metabolic syndrome (Keogh & MacLeod, 2012; Wall et al., 2017). In addition, those on ADT can suffer a decrease in bone mineral density, resulting in a high risk of fractures and therefore further impacting physical function. A recent paper produced recommendations for exercise as part of the treatment and management of metastatic prostate cancer, to help reduce the impact on physical function (Figure 2) (National Institute for Health and Care Excellence, 2014b).

2.9.2 Impact of Treatment on Health-related Quality of Life

While survival rates and improving surgical margins are critical goals in the treatment of prostate cancer, the impact of treatment on quality of life is

another consideration. Changes in body composition can negatively influence quality of life, but prostate cancer patients can also suffer from depressive symptoms, sexual dysfunction, urinary incontinence and gynecomastia, which all effect mental state and health-related quality of life.

After surgery men often suffer with urinary incontinence and erectile dysfunction as a direct result of the operating procedure (Bang & Almallah, 2016; Jones et al., 2014; Lardas et al., 2017; Lehto et al., 2017). It has been noted that exercise may reduce the risk of urinary incontinence by increasing muscle mass, thereby facilitating bladder and pelvic floor control, whereas being overweight/obese may increase the risk due to increased strain and pressure on the bladder (Wolin, Luly, Sutcliffe, Andriole, & Kibel, 2010). The robot-assisted radical prostatectomy procedure regularly results in impotence (75%), whereas this is much less (approximately 51-67%) in other treatments (i.e. radiotherapy, brachytherapy, ADT, active surveillance). Approximately 32% of all surgical patients report permanent sexual dysfunction (Lehto et al., 2017). It has been suggested that those receiving robot-assisted radical prostatectomy as a treatment option tend to be younger and more likely to have a sex life before treatment, therefore the impact of the surgery on sexual dysfunction has a far greater impact upon the patient and their partner's quality of life (Lehto et al., 2017). The pathophysiology of erectile dysfunction post robot-assisted radical prostatectomy involves both neuronal and vascular endothelial cell dysfunction, which therefore lead to compromised penile tissue oxygenation and smooth muscle apoptosis, fibrosis, and veno-occlusion dysfunction (Jones et al., 2014; Watts, Chew, & Stuckey, 2007). ADT is also reported to induce sexual dysfunction and in some cases urinary incontinence, however, there is much less research into these issues with regard to health related quality of life (Cormie et al., 2015; Lehto et al., 2017).

A recent longitudinal study explored quality of life and mood in patients treated with robot-assisted radical prostatectomy. The authors found that patients who reported being physically active, having low alcohol consumption and being non-smokers experienced lower risks of impaired quality of life, negative thoughts about the prostate cancer and depressed mood compared with

patients who were physically inactive, had high alcohol consumption and were current smokers (Bock et al., 2017). This therefore provides a rationale for more research into improving health behaviours before, during and after treatment through lifestyle changes whether that be diet, smoking cessation or exercise interventions.

Additionally, in both surgical and ADT patients it is suggested that fatigue may act independently on quality of life but may also contribute to sexual dysfunction and a loss of self-esteem (Fosså et al., 2016). Due to a reduction in quality of life, alongside prostate cancer survivors experiencing a greater number of recurrent admissions and associated medical comorbidities, it is important to develop screening or preventive strategies such as exercise programmes as part of the treatment to reduce readmissions for this group of cancer survivors (Gnanaraj et al., 2017).

2.9.3 The Role of Exercise Training for Prostate Cancer Patients

There is a growing base of evidence that suggests engaging patients in exercise throughout the cancer continuum, leads to fewer symptoms and side effects, and reduces the rate at which physiologic systems are affected (Brown, Winters-Stone, Lee, & Schmitz, 2012). In this way, exercise can be used as an adjunct therapy to cancer treatments to help alleviate some of the side effects. Providing patient care however, produces many competing demands for clinicians and therefore it is unrealistic for clinicians to stay well-informed of all the literature relating to cancer pathology, treatment modalities and exercise rehabilitation.

Exercise after cancer treatment can benefit patients through both the physiological adaptations to exercise training and by reversing deconditioning that can begin at diagnosis and persist long into the recovery period. The majority of studies investigating exercise in cancer patients have used aerobic exercise to improve patient outcomes with few exploring the benefits of RET (Ashcraft, Peace, Betof, Dewhirst, & Jones, 2016; Courneya, McNeil, O'Reilly,

Morielli, & Friedenreich, 2017; Jones et al., 2014; Tian, Lu, Lin, & Hu, 2016; Windsor, Nicol, & Potter, 2004; Zopf et al., 2017). A systematic review conducted in 2016 suggested that those studies which do utilise RET are very generic and in a relatively heterogenous population and concluded that more interventions are required to apply the principles of RET, along with clear reporting of intervention characteristics (C M. Fairman, Hyde, & Focht, 2017). Specifically for prostate cancer patients after robot-assisted radical prostatectomy, preliminary evidence suggests that exercise training can improve quality of life, cancer-related fatigue, erectile function, cardiorespiratory fitness and strength, however there are limited studies that exist solely within this population (Bourke et al., 2016; Silva, Sousa, Azevedo, & Martins, 2017).

2.10 Guidelines for Exercise Treatment

NICE currently recommend exercise but have no published guidelines on exercise during or after cancer treatment despite several studies demonstrating that exercise is safe, enhances quality of life and can potentially reduce some of the side effects associated with treatment (National Institute for Health and Care Excellence, 2014a). Commonly, doctors recommend that patients try to meet general Government guidelines on physical activity (Sutton et al., 2017). These guidelines state that healthy adults aged 19-64 years should complete at least 150 minutes (2½ hours) of moderate intensity aerobic activity in bouts of 10 minutes or more over the course of a week alongside muscle strengthening activities on at least 2 days a week (Department of Health, 2011). Patients also often receive information produced by Prostate Cancer UK which offers brief advice, generally following Government guidelines regarding physical activity (Prostate Cancer UK, 2015).

The ACSM has produced guidelines for exercise in cancer patients however these currently do not translate into UK healthcare practice. The ACSM recommends that cancer patients should avoid being inactive during and after

treatment and should undertake aerobic exercise such as walking, cycling and swimming as well as RET (e.g. weights, resistance bands and weight-bearing tasks) and flexibility exercise (Riebe et al., 2017). ACSM suggest that physical activity should be increased to 3-5 days a week over the course of one month, with RET being incorporated into a routine on 2-3 days a week. Despite a lack of clarity on the frequency, intensity and type of exercise that is safe and effective for cancer patients, numerous studies (Bloomquist et al., 2016; Cormie et al., 2016; Cunningham et al., 1986; C. M. Fairman, LaFountain, Lucas, & Focht, 2017) have explored these variables in multiple cancer populations.

2.11 Exercise Advice Provided by Health Care Professionals

There is currently a lack of research investigating exercise prescription and health care professionals' opinions of exercise as part of the patient pathway of care. However, NICE recommends structured exercise programmes tailored to individual needs to manage, and for rehabilitation after, certain health conditions, such as myocardial infarction, stroke, chronic heart failure, chronic obstructive pulmonary disease, depression, lower back pain and chronic fatigue syndrome (National Institute for Health and Care Excellence, 2014a). Despite this, there are no published guidelines for exercise programmes in patients who have been diagnosed with, or treated for, prostate cancer despite it being recommended by NICE. A study in 1997 reported that a publicly funded programme of regular moderate intensity exercise for adults < 65 years old could achieve important health benefits at relatively low cost (Munro, Brazier, Davey, & Nicholl, 1997). Further studies in 2011 and 2012 suggested that exercise programmes are associated with modest benefits but are highly dependent on patient's adherence (Anokye et al., 2011; Murphy et al., 2012).

Prostate cancer patients have reported several barriers to taking part in exercise programmes such as lack of clinical advice, poor weather, lack of knowledge on the benefits of exercise, treatment side effects (i.e. urinary incontinence) and time pressures (Hackshaw-McGeagh et al., 2017). Despite

this, patients have expressed an interest in receiving exercise advice from health care professionals. A recent study indicated that whilst few health care professionals advise on exercise for prostate cancer patients, those who did only provided advice aligning with the Department of Health's guidelines for adults (Sutton et al., 2017). Such recommendations may be inadequate as the guidelines are for adults who are assumed to be healthy and not tailored to the specific needs of prostate cancer patients. In spite of a lack of evidence for prostate cancer specific exercise prescription, many health professionals agree that exercise should be tailored to individual patient's pre-treatment level of fitness, current health, mobility problems, treatment received, and their stage in the treatment process (Sutton et al., 2017).

A prostate cancer diagnosis has been previously described as a 'teachable moment' in which patients become motivated to reduce unhealthy behaviours, especially if the advice is delivered by a trusted source such as a health care professional (Horwood et al., 2014; McBride, Emmons, & Lipkus, 2003; Sutton et al., 2017). Therefore, the diagnosis of prostate cancer presents an opportunity to implement and engage patients in exercise interventions. Despite health care professionals being well-placed to deliver exercise advice, a survey commissioned by Macmillan Cancer Support in 2011 reported that 72% of GPs and 60% of oncologists do not discuss exercise with patients (Macmillan Cancer Support, 2011). More recently it was reported that fewer than half of cancer specialists in the United Kingdom regularly discuss exercise with prostate cancer patients (Sutton et al., 2017). Furthermore, a study conducted in Australia reported few doctors recommend exercise and when they do the importance is on aerobic exercise (59%) rather than RET (13%) (Short et al., 2016). This data may demonstrate some naivety amongst health care professionals on the benefits of exercise in preventing, managing or reducing disease reoccurrence. Health care professionals have cited reasons including a lack of personal expertise, training and services to support exercise, with others simply reporting a lack of time (Cowan, 2016; Fortier, Guerin, & Segar, 2016; Sutton et al., 2017).

To reduce some of the side effects and long-term effects of the disease and treatment, exercise advice and prescription needs to be more readily available to patients. There also needs to more consistency across the country as currently exercise referral programmes are available in some NHS Trusts but not in others. Furthermore, health care professionals need more information and training on exercise advice and prescription to prostate cancer patients through better dissemination of research to governing bodies and societies (Macmillan Cancer Support, 2011). It is hoped that this may be improved through the 2015 launch of Exercise Medicine resources for use in teaching on medical degree programmes (Gates, 2015, 2016).

2.12 Exercise for Alleviating the Effects of Prostate Cancer Treatment

With both surgery and ADT causing side effects and functional decline, exercise can be used as a countermeasure to the side effects of treatment. It has been suggested that regular exercise can reduce disease symptoms, improve quality of life and side effects of the treatments and help to reduce disease reoccurrence (Hart, Galvao, & Newton, 2017). For example, erectile dysfunction, a major side effect of robot-assisted radical prostatectomy, is linked to reduced aerobic capacity and, in ADT patients, adverse cardiovascular risk profile (Jones et al., 2014; Watts et al., 2007). The use of exercise as part of the treatment pathway for prostate cancer has been explored in a recent systematic review (Moe et al., 2017). The review demonstrated that exercise should be considered an important component of prostate cancer care and that it is generally safe and well tolerated in such a population (Moe et al., 2017).

The majority of research within clinical populations has focused on aerobic exercise. The benefits of aerobic exercise, with and without dietary advice, to prostate cancer patients has been studied extensively in recent years, with the most common benefits including improved peak oxygen uptake and physical functioning and, decreased levels of fatigue and depression (Eriksen et al., 2017; Hvid et al., 2016; Jones et al., 2014; Martin, Battaglini, Hands, &

Naumann, 2015; Park et al., 2012; Segal et al., 2009; Shingler et al., 2017). The health benefits of RET in clinical populations, however, are far less extensively researched. The benefits of RET are becoming increasingly recognised with some including those that have traditionally been unique to aerobic training e.g. improved cardiorespiratory fitness (Steele et al., 2017). Some studies demonstrate that RET can result in longer-term health benefits compared to aerobic exercise when undertaken 2-3 days a week for 12 weeks (Baumann, Zopf, & Bloch, 2012; Champ, Francis, Klement, Dickerman, & Smith, 2016; Teleni et al., 2016). Many papers have attempted to use RET as a vehicle for improving strength, power and muscle mass in various different populations, including prostate cancer patients (Bechshoft et al., 2017; Lourenzi et al., 2017; Nilsen et al., 2015; Schoenfeld, Wilson, Lowery, & Krieger, 2016). Along with reducing feelings of depression and fatigue, regular RET can improve muscle strength and endurance, quality of life and even cardiorespiratory fitness, as well as reduce blood pressure and waist circumference after prostate cancer treatments (Baumann et al., 2012; Galvao et al., 2006; Hasenoehrl et al., 2015; Santa Mina, Connor, et al., 2013; Segal et al., 2009).

2.12.1 Mechanisms for Benefits of RET for Prostate Cancer

Mechanisms for the effects of RET on cardiovascular health and the side effects of those treated for prostate cancer via robot-assisted radical prostatectomy or ADT include endothelial function, microvascular changes affecting the skeletal muscle (i.e., angiogenesis) and macrovascular changes to the arterial tree (i.e., arteriogenesis). RET may also be used as a vehicle for improving other markers of cardiometabolic health, including central cardiovascular fitness, cardiometabolic health and skeletal muscle adaptions.

2.12.2 Endothelial Function

An important factor related to both micro and microvascular adaptation to exercise is endothelial function. Dysfunction of the endothelium is not only a marker of the impairment due to risk factors of CVD acting on the arterial wall but is also a marker of the initiation and progression of atherosclerosis (Deanfield, Halcox, & Rabelink, 2007). Normal vascular endothelial function can be restored through both pharmaceutical treatment (e.g. statins) and exercise (Fiuza-Luces et al., 2018). A meta-analysis, conducted in adults, found that aerobic exercise improves vascular endothelial function in a dose-dependent manner, with every 2 MET increase in intensity approximately associated with a 1% improvement in FMD (Ashor et al., 2015). Furthermore, the studies included in the review demonstrated that aerobic, resistance and combined exercise modalities increased FMD by approximately 2%, potentially leading to a reduction in CVD risk of about 20% (Ashor et al., 2015). Ultrasound assessment of endothelial function using flow mediated dilatation (FMD) is a safe, inexpensive, non-invasive methods of assessing vascular health and predicting the risk of future cardiovascular events (Deanfield et al., 2007; Thijssen, 2011). The term FMD simply describes arterial vasodilation following an increase in luminal blood flow and resulting internal-wall shear stress (Thijssen, 2011). It is important to note the importance of nitric oxide, released from vascular endothelium, as a potent vasodilator and the anti-atherogenic properties it possesses. Shear stress on the endothelial cells is a physiological stimulus to nitric oxide production and, although the role of endothelium-derived nitric oxide in acute exercise is not fully understood, prolonged repetitive exercise training up-regulates endothelial nitric oxide bioactivity (Deanfield et al., 2007; Daniel J. Green et al., 2003; Maiorana, O'Driscoll, Taylor, & Green, 2003; Niebauer & Cooke, 1996; Thijssen, 2011). A meta-analysis examining evidence from 14 studies demonstrated that for each 1% increase in FMD, the relative risk of suffering a cardiovascular event is reduced by 13% (Inaba, Chen, & Bergmann, 2010). Measurements of endothelial function via FMD are sensitive to changes in various cardiovascular risk factors such as plasma lipids, blood glucose and body composition, which can be altered favourably through exercise. Therefore, FMD might provide a suitable

method to evaluate changes in cardiovascular risk in men being treated for prostate cancer via robot-assisted radical prostatectomy or ADT.

2.12.3 Angiogenesis

Angiogenesis is stimulated through hypoxic and mechanical factors and is the process by which new blood vessels form from a pre-existing vascular bed and plays a critical role in tissue growth and repair (Heil, Eitenmuller, Schmitz-Rixen, & Schaper, 2006; Rizzi, Benagiano, & Ribatti, 2017).

There are multiple cytokines involved in angiogenesis but vascular endothelial growth factor (VEGF) appears to be central in the initiation of the process. VEGF is released from the small vessels involved in angiogenesis and stimulates endothelial cell proliferation and migration as well as being essential in the maintenance of muscle capillarity (Bloor, 2005). Interestingly, angiogenesis is also a fundamental part of the development of prostate cancer progression and metastasis (Russo, Mischi, Scheepens, De la Rosette, & Wijkstra, 2012). Tumour cells can induce new blood vessels by producing VEGF, which is expressed by most cancer types including prostate cancer (Russo et al., 2012; Yu & Rak, 2003). In patients with prostate cancer treated via ADT the progression of cancer and therefore angiogenesis is somewhat reduced or slowed down. However, with both ADT and surgery for prostate cancer muscle wastage is common and exercise can be used to induce angiogenesis in the affected musculature and thereby countering the adverse effects of these prostate cancer treatment. Exercise induces changes in skeletal muscle through hypoxia resulting in increased vascular cell proliferation, muscle capillarity and the diameter of large conduit arteries (Bloor, 2005). At the tissue level, exercise increases flow capacity and capillary surface area (Bloor, 2005).

The degree to which hypoxia, initiated through exercise, stimulates capillary angiogenesis remains unclear however, hypoxia is known to promote the upregulation of VEGF. VEGF stimulates the proliferation and migration of endothelial cells by binding to VEGF receptors which are expressed on the endothelial cell surface thereby producing microvascular changes (Yu & Rak,

2003). Because the expression of VEGF is reduced with increasing age, exercise-induced angiogenesis is likely to be impaired in men of advanced age who suffer muscle wastage due to prostate cancer treatments. This being said, exercise training at high intensities may improve the age induced downregulation of VEGF (Iemitsu, Maeda, Jesmin, Otsuki, & Miyauchi, 2006; Korivi, 2010). Therefore, regular exercise may be an effective stimulus for angiogenesis in normal physiological and pathological conditions.

2.12.4 Arteriogenesis

Arteriogenesis is the remodelling of current collateral arteries and arterioles into arteries, resulting in an increased diameter, and is influenced by physical forces, most importantly shear stress combined with the upregulation of key enzymes such as nitric oxide and VEGF (Heil et al., 2006; Helisch & Schaper, 2003; Rizzi et al., 2017).

Despite extensive research on angiogenesis and its interactions as a result of tumour growth and exercise, there has been little on vascular remodelling upstream of active angiogenesis at a tumour site. It has been suggested that due to angiogenesis of the capillary bed during cancerous tumour growth, there is concurrent expansion of the upstream arterioles (Yu & Rak, 2003). Moreover, muscle loading through RET has been reported as increasing the number and length of distal arterioles with an extension of the arteriolar tree (Hansen-Smith, Egginton, Zhou, & Hudlicka, 2001). Therefore exercise, particularly RET, may play a key part in reducing the CVD risk in men with prostate cancer, treated via surgery or ADT, by increasing the rate of arteriogenesis. Prostate cancer patients are at increased risk of CVD (Allott et al., 2013) and exercise can improve the utilization and extraction of oxygen from erythrocytes, influence blood viscosity, and help inhibit the progression of atherosclerosis (van Royen et al., 2001).

2.12.5 Blood Borne Biomarkers of Cardiometabolic Health

Unfavourable levels of blood lipids, glucose and insulin are associated with the development of CVD and metabolic syndrome. It is therefore important that these risk markers are managed through a combination of pharmaceutical interventions and lifestyle alterations. Due to the average age of men diagnosed with prostate cancer being > 65 years of age, it is common that they also present with comorbidities such as hyperlipidaemia or diabetes that put them at an increased risk of developing CVD. Furthermore, blood lipid levels may increase in the weeks post-surgery due to patients being sedentary. ADT may also cause increases in blood lipid profile due to the increase in fat mass which often accompanies this treatment approach.

RET can improve body composition by increasing lean body mass and reducing fat mass. The resulting changes in body composition from RET are thought to have a positive impact upon insulin resistance and blood glucose levels. Glucose is an important fuel for contracting muscle, and normal glucose metabolism is vital for health. Glucose transporter type 4 (GLUT-4) is an insulin-regulating protein responsible for glucose transportation into skeletal muscle. Muscle glucose uptake relies on GLUT-4 and exercise is the most potent stimulator on GLUT-4 expression. This in turn can contribute to improved insulin control, glucose synthesis and enhanced muscle glycogen storage following RET (Azarbayjani, Abedi, Peeri, Rasaee, & Stannard, 2014; Richter & Hargreaves, 2013; Sañudo et al., 2013). An increase in skeletal muscle mass can also improve blood lipid profile by increasing the capacity of the muscles to utilise lipids as a fuel (rather than glycogen) and increasing lipoprotein lipase activity (Laaksonen et al., 2000; Mann, Beedie, & Jimenez, 2014).

2.12.6 Cardiorespiratory Fitness

Cardiorespiratory fitness declines with age, physical inactivity and sedentary behaviour. Individuals achieving moderate-to-high cardiorespiratory fitness

levels (i.e. ≥ 8 METs) have been associated with a reduced risk of CVD events (Kodama et al., 2009). Additionally, it has been suggested that an increase in cardiorespiratory fitness of only 1 MET could decrease the risk of CVD by 15% (Fiuza-Luces et al., 2018; Kodama et al., 2009).

A limited body of evidence suggests that RET has the potential to improve cardiovascular risk markers, as well as attenuating age- and chronic-disease-related skeletal muscle loss/sarcopenia, which could potentially impact peak rate of oxygen consumption ($\dot{V}O_2$Peak) by increasing oxygen utilisation capacity. Muscle oxidative capacity is reduced in ageing by a reduction in muscle mass and mitochondrial density, influencing the age-related decline in $\dot{V}O_2$Peak (Frank et al., 2016). This is of particular importance for those aged >50 years as age-related physiological changes, including increases in blood pressure, arterial stiffness and fat mass (with associated changes in systemic physiology) coupled with reductions in $\dot{V}O_2$Peak increase the risk of premature cardiovascular mortality, particularly in inactive older people (Cornelissen, Fagard, Coeckelberghs, & Vanhees, 2011; Hollings, Mavros, Freeston, & Fiatarone Singh, 2017; Moro et al., 2017; Otsuki, 2006).

Contrary to traditional opinions, several papers have been recently reported an increase in $\dot{V}O_2$Peak after RET programmes in both healthy elderly and clinical populations (Frank et al., 2016; Hunter, McCarthy, & Bamman, 2004; Osteras, Helgerud, & Hoff, 2002). Frank and colleagues (Frank et al., 2016) suggested that RET is effective in reversing the age-related decline in cardiorespiratory capacity due to a shift in muscle fibre type composition and an increase in mitochondrial biogenesis and proteins. Such changes could be due to: (1) the high frequency of training sessions (3 sessions a week), (2) high intensity which increased progressively and, (3) an increase in work economy that can be partly explained by enhanced changes in the force-velocity relationship and improved mechanical power output (Frank et al., 2016; Hunter et al., 2004; Osteras et al., 2002). The use of RET has recently been explored in a systematic review of patients undergoing cardiac rehabilitation programmes and similar improvement in $\dot{V}O_2$Peak were apparent in RET and

aerobic exercise groups when compared to a non-exercise control group (Hollings et al., 2017).

2.12.7 Skeletal Muscle Adaptation

Sarcopenia is an often overlooked as a cardiometabolic risk factor that can be in the most-part reversed through RET (Fiuza-Luces et al., 2018). It is a common condition in cancer patients, regardless of disease stage, and is associated with higher mortality rates in both advanced stage (Tan, Birdsell, Martin, Baracos, & Fearon, 2009; van Vledder et al., 2012) and early-stage patients (Villasenor et al., 2012). RET constitutes an effective modulator of skeletal muscle function with a growing body of evidence supporting the safe and effective use in prostate cancer patients in whom it has much potential to improve muscle mass and function (Christensen et al., 2014; C. M. Fairman et al., 2017; Hasenoehrl et al., 2015; Keilani et al., 2017; Norris, Bell, North, & Courneya, 2015).

Skeletal muscle produces and releases myokines into the blood, particularly during muscular contraction, where they function to elicit countless benefits, including decreased inflammation and insulin resistance (Fiuza-Luces, Garatachea, Berger, & Lucia, 2013). Interleukin-6 (IL-6) is a pro-inflammatory cytokine that when elevated is associated with type 2 diabetes mellitus and intima-media thickness (Chen et al., 2017; B. Zhang et al., 2015). However, when released by contracting muscles during exercise IL-6 can induce healthy metabolic effects such as increasing lipolysis and fat oxidation in adipose tissue and reducing skeletal muscle insulin resistance (Lambernd et al., 2012; Pedersen & Febbraio, 2008).

In addition to micro- and macro-vascular adaptions following RET programmes, skeletal muscle adaptions include improvements in muscle strength, muscle mass and endurance. A recent study which assessed lean body mass, via a dual x-ray absorptiometry (DXA), showed that despite no changes in trunk lean body mass, both lower and upper extremity lean body

mass improved significantly after 16 weeks of RET (Nilsen et al., 2015). One particular study in 2013 which examined the effects of 12 weeks of RET in men on ADT reported significant increases in total body muscle mass (2.7%), power (17%), and strength (28%) as well as significant increases in functional performance (20%) and muscle endurance (110%) (Hanson et al., 2013). Another study showed that prostate cancer patients improved upper and lower body strength by 22% and 24%, respectively, following 24 weeks of RET (Segal et al., 2009). Furthermore, skeletal muscle is the major site of dietary glucose utilisation and therefore increasing muscle mass can contribute to a reduced risk of insulin resistance (Fiuza-Luces et al., 2018). Such improvements in skeletal muscle not only help improve quality of life through increase ability to complete activities of daily living but also help to reduce the likelihood of falls and risk of metabolic syndrome (Fiuza-Luces et al., 2018; Frank et al., 2016).

2.13 Supervised Versus Home-based Exercise

The benefits of supervised RET have been extensively reported and include improvements in lean body mass, muscle strength, aerobic capacity and blood lipid profile (Andersen, Schmidt, Pedersen, Krustrup, & Bangsbo, 2016; DeVallance et al., 2016; Fahlman, Boardley, Lambert, & Flynn, 2002). However, such research has been largely investigated in supervised groups using gym equipment, which is resource- and time-intensive for both the patient and the NHS. The estimated cost per patient for supervised exercise referral programmes in the NHS is £229 per person, which is based on a health technology assessment and inflation indices from the Personal Social Services Research Unit (F. Campbell et al., 2015; Curtis, 2011; Isaacs et al., 2007). This figure rises each year and could incur extra costs depending upon the comorbidities of the patients and the geographical area of implementation (F. Campbell et al., 2015). Due to the associated costs of supervised exercise referral programmes, there is some uncertainty surrounding the cost effectiveness of the programmes.

However, studies have reported that exercise interventions reduce fatigue, improve immune function and improve quality of life in prostate cancer patients who have undergone robot-assisted radical prostatectomy or ADT (Courneya et al., 2004; Galvao et al., 2006; Hojman, 2017; Park et al., 2012). In addition, aerobic exercise has been reported to improve peak oxygen uptake and decrease fatigue, reduce depression and prevent deterioration in physical function during treatment for prostate cancer (Jones et al., 2014; Keogh & MacLeod, 2012; Park et al., 2012; Storer et al., 2012). RET interventions are also effective for reducing fatigue and depression and may bring about more beneficial effects compared to aerobic training in relation to outcomes such as muscle strength, quality of life and well-being, as well as reductions in blood pressure and waist circumference after prostate cancer treatments (Baumann et al., 2012; Mustian et al., 2009; Segal et al., 2009). This body of research suggests that more exercise studies which include cost-effectiveness analysis are warranted.

Maintaining regular exercise can be difficult for cancer patients due to cancer-related fatigue and lack of clear information about exercise and its benefits (Fernandez et al., 2015). Other challenges to regular exercise include financial and environmental factors. However, investigations into the barriers to exercise have mainly focused on breast cancer survivors, with much less known about the barriers in other cancer populations (Nock et al., 2015; Ottenbacher et al., 2011). Fatigue and deconditioning as a result of cancer treatment can present physical barriers which may lead to social isolation and lack of regular exercise (Fernandez et al., 2015). Other studies have reported lack of time, enjoyment and treatment side effects as barriers to exercise in cancer survivors (Craike, Livingston, & Botti, 2011; Fernandez et al., 2015; Hefferon, Murphy, McLeod, Mutrie, & Campbell, 2013; Ottenbacher et al., 2011; Spector, Battaglini, & Groff, 2013). A study by Ottenbacher and colleagues (Ottenbacher et al., 2011) showed that lack of will power and the weather can be important barriers to exercise participation after prostate cancer treatment. Studies have explored behaviour change techniques to promote exercise in patients living with and after cancer. A recent systematic

review demonstrated that those exercise interventions with the better adherence levels share some common characteristics (Bourke et al., 2013; Turner et al., 2018). Such characteristics include setting goals, promoting self-monitoring and, encouraging patients to attempt behaviour learnt in a supervised setting in a non-supervised/home setting (Bourke et al., 2013; Greaves et al., 2011; Turner et al., 2018). Clinical populations already studied in home-based programmes include those with heart failure, prostate and breast cancer patients, type 2 diabetics, and those with osteoarthritis and good adherence rates have been demonstrated (Bruce-Brand et al., 2012; Hvid et al., 2016; Mustian et al., 2009; Plotnikoff et al., 2010; Safiyari-Hafizi, Taunton, Ignaszewski, & Warburton, 2016). Therefore, home-based training incorporating goal setting whilst maintaining or tapering a level of supervision may be more appropriate and cost-effective than fully supervised exercise for both the NHS and the patient.

Although supervised RET interventions have the potential to generate longer-term improvements (~6 months) in health when compared to aerobic exercise or standard care (Ashton et al., 2018; Baumann et al., 2012; Segal et al., 2009), it is unlikely to be feasible for the NHS to implement or the patient to adhere to over a long period (Park et al., 2012; Segal et al., 2009). However, the health benefits gained from supervised RET have been shown to be sustained by a subsequent a home-based exercise programme (Galvao et al., 2014). Home-based RET programmes with continued support might help to overcome some of the barriers to exercise participation in prostate cancer survivors, as well as providing a low cost alternative to supervised RET programmes but to help to maintain adherence, the use of goal setting and self-monitoring should be incorporated (Bourke et al., 2013, 2014; Bruce-Brand et al., 2012; Craike et al., 2011; Moe et al., 2017; Thiebaud, 2014).

2.14 Conclusion

In summary, progressive RET may facilitate improved cardiometabolic health and side effects of prostate cancer treatment, specifically robot-assisted

radical prostatectomy. Relevant beneficial physiological effects of RET include improved erectile dysfunction, cardiorespiratory fitness, muscle mass, blood biomarkers and attenuation of fatigue, fat mass, and arterial endothelial dysfunction. Appropriate RET programmes may be partially supervised but primarily take place in the home environment to help counteract some of the barriers to participation. Further research is clearly needed in the area of RET for patients treated for prostate cancer via robot-assisted radical prostatectomy.

CHAPTER 3

SYSTEMATIC REVIEW

3.0 Effects of short-, medium- and long-term resistance training on measures of cardiometabolic health in adults: a systematic review and meta-analysis

3.1 Introduction

Cardiovascular disease is a substantial human and economic burden, responsible for 17.7 million deaths globally in 2015 (World Health Organisation, 2017). The positive impact of regular moderate to vigorous intensity aerobic exercise (e.g. brisk walking, jogging, cycling) on cardiometabolic health, including improvements in cardiopulmonary exercise capacity, blood pressure, glycaemic control, hypercholesterolemia and vascular endothelial function (Chodzko-Zajko, 2009; Otsuki, 2006), is well-documented and recognised in current UK and global physical activity recommendations (UK Chief Medical Officers' Guidelines, 2011; World Health Organisation, 2010). However, while the health benefits of regular resistance exercise training (RET) in relation to maintaining skeletal muscle size and strength are also recognised in current physical activity recommendations, the role of RET in enhancing cardiometabolic health is less well defined.

RET is characterised by muscular activities working against an external load and may be easier than aerobic exercise to implement and sustain in the home environment as it offers an alternative way to exercise for older adults who have limited space or access to equipment and time availability (Galvao et al., 2014; King, Haskell, Taylor, Kraemer, & DeBusk, 1991; Thiebaud, 2014). Most studies of RET have focused on changes in skeletal muscle size and strength, with few investigating cardiometabolic health effects as primary outcomes although several have reported cardiometabolic variables as secondary outcomes (Liu & Latham, 2009; Raymond, Bramley-Tzerefos, Jeffs, Winter, & Holland, 2013; Thiebaud, 2014).

There is preliminary evidence that RET may positively alter blood lipid profile, body composition, systolic blood pressure (Gerage et al., 2013; James et al.,

2016; Moro et al., 2017), circulating inflammatory markers and cardiopulmonary exercise capacity (De Salles, 2010; Kelley & Kelley, 2010; Otsuki, 2006). RET may also generate longer-lasting improvements in body fat, fasted insulin, lipid profile and systolic blood pressure than aerobic exercise (Segal et al., 2009; Sigal et al., 2007). Finally, RET may have an important role in attenuating age-related physiological changes such as increases in systolic blood pressure and arterial stiffness, and the reduction of skeletal muscle mass (with associated changes in systemic physiology) (Chodzko-Zajko, 2009; Straight, 2016).

Aside from the lack of RET intervention studies with a primary focus on cardiometabolic health outcomes, interpreting the impact of RET on cardiometabolic health is constrained by heterogeneity of methodology, including the duration of interventions and populations. High-quality systematic reviews and meta-analyses can help to overcome these challenges, while accounting for bias and heterogeneity, by providing more precise estimates of effect size changes. The aim of this systematic review was to assess the effects of short-, medium- and long-term RET programmes compared to control or usual care on cardiometabolic health outcomes in adults.

3.2 Methods

This systematic review was prospectively registered in an international database of systematic reviews in health and social care (registration number CRD42016037946; http://www.crd.york.ac.uk/PROSPERO/). The preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines were followed to guide the reporting of this review (Moher, 2015).

3.2.1 Eligibility Criteria

We included randomised controlled trials (RCTs) published in English that compared any RET programme alone to a non-exercising control or usual care group. Participants must have been aged ≥ 18 years, non-athletic (World

Health Organisation, 2013), and recruited to a RET programme (e.g. elastic resistance band, weight machines, etc.) of at least 2 weeks duration, irrespective of intensity or frequency that was conducted in any setting (e.g. home, hospital). We included studies where isometric RET with whole body vibration was used. We excluded studies where RET interventions were combined with other lifestyle components or exercise modes (e.g. aerobic exercise, diet, etc.) to isolate the effects of RET. Studies that included at least one of the following cardiometabolic health outcomes or clinical end-points were eligible: $\dot{V}O_2$Peak; flow-mediated dilatation; C-reactive protein; total cholesterol; high-density lipoprotein cholesterol; low-density lipoprotein cholesterol; triglycerides; fasted glucose; fasted insulin; insulin resistance (HOMA-IR); resting blood pressure; mean arterial pressure; resting heart rate; cardiovascular mortality; all-cause mortality; non-fatal end-points (e.g. myocardial infarction, coronary artery bypass grafting; percutaneous transluminal coronary angioplasty; angina or angiographically-defined coronary heart disease; stroke; carotid endarterectomy; peripheral arterial disease.

3.2.2 Search Strategy

The MEDLINE Ovid and Cochrane Library databases were searched from inception to February 2018. The search strategy keywords and MeSH terms used included: progressive resistance, strength training, exercise and randomised controlled trial. Details of the full search strategy can be found in Appendix 2a. Reference lists of all relevant systematic reviews identified were searched for additional studies. All searches were conducted by the same author (RA), with search results collated using EndNote software (Thomson Reuters, New York), and duplicates removed.

The first 10% of titles and abstracts were screened independently by two reviewers (RA and GT) and, due to good agreement, the remaining texts were screened by one reviewer only (RA, GT, JS or LL) (G. A. Tew, Brabyn, S., Cook, L., & Peckham, E. , 2016). Screening of full-texts was performed by two

independent reviewers (RA and GT) with disagreements resolved through consensus or a third reviewer being consulted (JS).

3.2.3 Data Extraction

Two authors (RA and SG) independently extracted data using Microsoft Excel. Any disagreements were resolved via consensus. When more than one publication was apparent for the same trial, data were collated (supplementary table 2). We extracted study design, participant demographics, intervention details and means and standard deviations for all outcomes. When necessary, published protocols and trial registries were searched for further methodological detail and risk of bias assessment. If there was insufficient information the authors (n = 40) were contacted via email. Resting blood pressure was expressed in millimetres of mercury (mmHg); resting heart rate in beats per minute (bpm), $\dot{V}O_2$Peak relative to body mass (ml/kg/min), flow-mediated dilatation as percentage, fasted insulin in micro units per millilitre (µU/ml), C-reactive protein in milligrams per litre (mg/L) and glucose, lipid profile and HOMA-IR in milligrams per decilitre (mg/dL). Adverse events were also extracted.

3.2.4 Risk of Bias

Risk of bias was assessed by two authors independently (RA and SG) using the Cochrane Risk of Bias tool (J. P. Y. Higgins, Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., Savović, J., Schulz, K.F., Weeks,L., Sterne, J.A.C., Cochrane Bias Methods Group & Cochrane Statistical Methods Group, 2011). Any disagreements were resolved through consensus. We judged risk of bias on the study level as ‘low’, ‘unclear’ or ‘high’ risk (S. P. T. Higgins, & Green, S., 2011). We used funnel plots to assess publication bias when there were more than 10 studies contributing data for an analysis (S. P. T. Higgins, & Green, S., 2011; A. J. Sutton, Song, F., Gilbody, S.M., & Abrams, K.R. , 2000). For all outcomes we conducted sensitivity analyses. For the sensitivity

analyses, we excluded studies that were judged as being at unclear risk of bias on the majority of domains on the Cochrane tool, or where at least 2 domains of the Cochrane tool were judged as being at high risk of bias before running the meta-analysis again.

3.2.5 Data Synthesis

Meta-analyses were undertaken using Review Manager (RevMan 5.3; Cochrane Collaboration, Oxford, UK) when more than two studies reported on the same outcome. In the pooled analysis of studies by duration, outcome data were organised into short-term (≤ 6 weeks), medium-term (7-23 weeks) and long-term (≥ 24 weeks) arbitrary categories. Where units of measurement could not be converted, standardised mean differences (SMD) were used. Data are presented as mean and 95% confidence intervals. The I^2 statistic was used to quantify statistical heterogeneity as follows: 0-40%: might not be important, 30-60%: moderate heterogeneity, 50-90%: substantial heterogeneity, 75-100%: considerable heterogeneity (S. P. T. Higgins, & Green, S., 2011). Fixed-effects models were used for analysis however, if statistical heterogeneity was noted ($I^2 > 40\%$), meta-analysis was performed using a random-effects model. The GRADE approach was used to assess the strength of evidence. Studies were downgraded if there were issues with risk of bias, consistency, precision or directness of the outcomes. The reasons for downgrading the evidence are outlined in Table 3.

Table 3. Criteria for downgrading the quality of outcomes using the GRADE approach.

	Reason to Downgrade the Level of Evidence
Risk of Bias	• Majority of studies rated as being at unclear risk of bias • Outcome includes studies that have been rated as being at high risk of bias in 2 or more categories
Inconsistency	• Large heterogeneity based on the similarity of point estimates, statistical heterogeneity and $I^2 \geq 50\%$
Imprecision	• Large confidence intervals when data are presented as standardised mean difference • Substantial heterogeneity ($I^2 \geq 50\%$) • If a recommendation or clinical course of action would differ if the upper versus the lower boundary of the confidence interval represented the truth • Sample size < 400 within the meta-analysis for each variable
Indirectness	• Use of surrogate outcomes
Publication Bias	• Asymmetric funnel plot

3.3 Results

3.3.1 Search Results

A total of 19,040 records were retrieved from database searches, of which 5,669 records were duplicates. A further 11,696 were then eliminated following screening of titles and abstracts (Figure 4). Sixty-three potentially relevant papers were identified from screening of systematic review reference lists (Figure 4). After full-text screening of 1,738 articles, 194 manuscripts from 173 RCTs were included in this review (Figure 4). Participants were individually randomised in all included trials (i.e. there were no cluster RCTs).

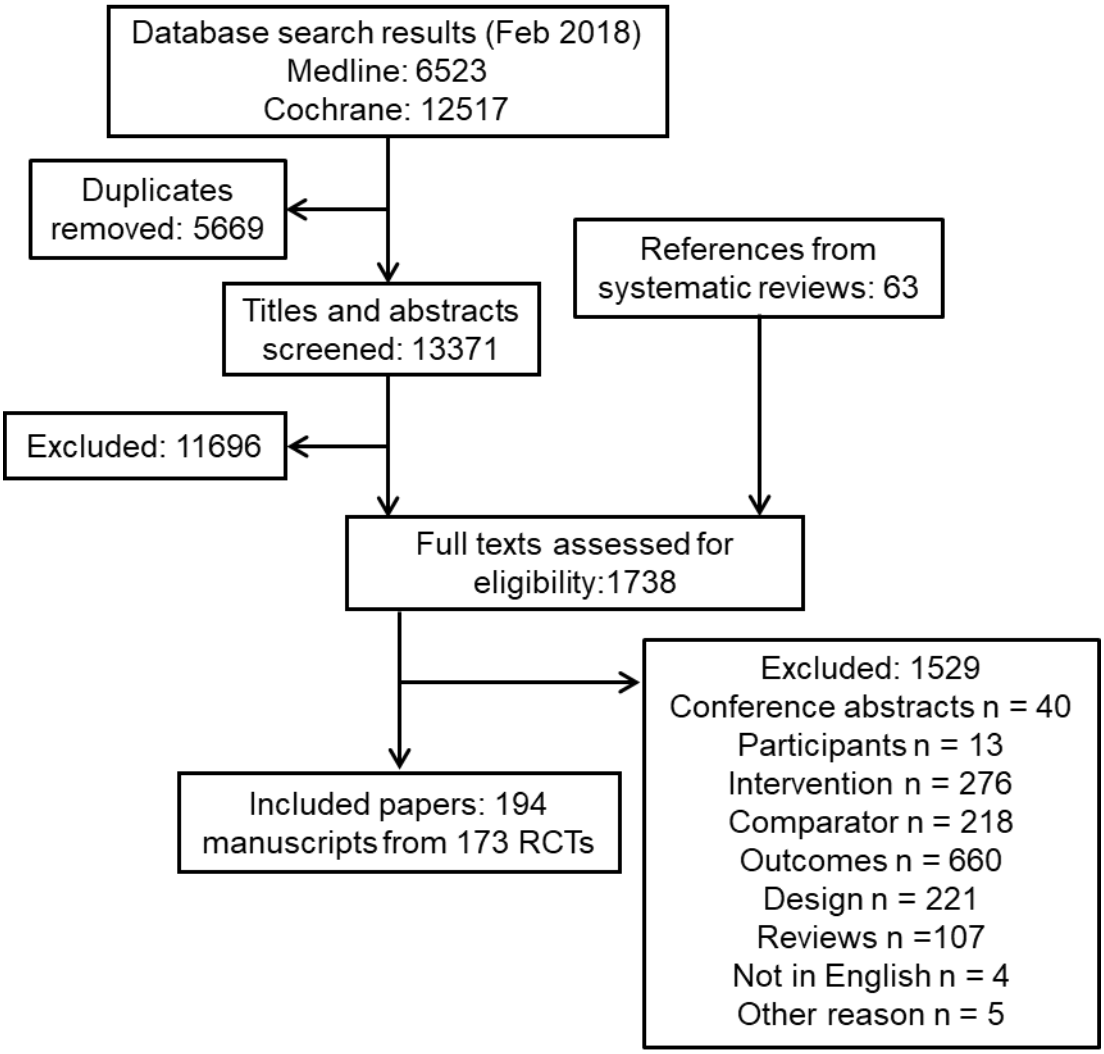

Figure 4. PRISMA flow diagram

3.3.2 Studies Included

The 173 RCTs comprised 6,169 participants (2,840 control and 3,329 RET participants), with sample sizes of 5-77 per group and 13-150 per study. One hundred studies involved healthy individuals and 73 studies involved clinical populations. All included studies were published between 1978 and February 2018. Summary details of the included trials and populations are presented in Appendix 2b and 2c respectively.

RET programmes mainly used weight machines (n = 90 studies; 52%), a mix of free weights, bodyweight and machine exercises (n = 43 studies; 25%),

elastic resistance bands (n = 13 studies; 8%), circuit exercises (n = 12 studies; 7%), free weights (n = 10 studies; 6%), ankle/leg weights (n = 2 studies; 1%), isometric hand grip (n = 2 studies; 1%) and isometric exercise with whole body vibration (n = 1 study).

The majority of interventions were supervised by an exercise professional (n = 105 studies; 61%). One study reported data from an unsupervised intervention, and 13 (8%) used a combination of supervised and unsupervised programmes. Fifty-four studies (31%) did not report the level of supervision.

The duration of the intervention varied from ≤ 6 weeks (n = 13), 7-23 weeks (n = 129) and ≥ 24 weeks (n = 31). The most common frequency of training was 3 sessions per week (n = 110), followed by 2 sessions per week (n = 36), though some studies required participants to complete the programme in 1, 4 or 5 sessions per week (n = 1, n = 7 and n = 5, respectively). The remaining studies stipulated either two-three sessions per week (n = 8), three-four sessions per week (n = 1) or did not report the frequency (n = 5).

In the majority of studies, control participants were instructed to continue with their habitual activity (n = 115/173) or were allocated to usual care (n = 15). Three studies provided lifestyle advice to the control group and discussion about physical activity levels, but no structured/supervised exercise (n = 3). Forty studies did not report the requirements of the control group. The included studies did not report any clinical end-points. A summary of the quality of evidence, based on risk of bias, study design, confidence intervals and variability in results, has been collated using the GRADE approach (Table 4).

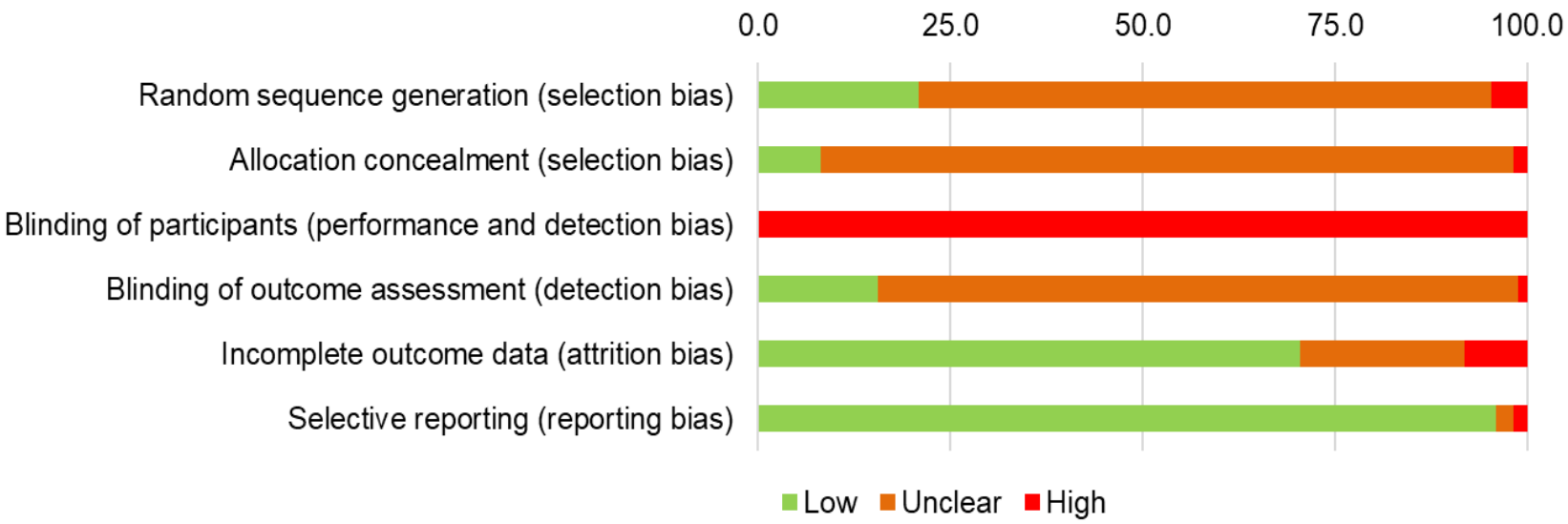

Figure 5. Risk of bias summary

3.3.3 Risk of Bias

Figure 5 shows a summary of the risk of bias decisions made per category for the included studies. Appendix 2d describes risk of bias for each study in more detail.

3.3.3.1 Selection Bias

An acceptable method of random sequence generation (i.e. computer generated) was used in 36 studies, 8 studies were judged as being at high risk of bias and the remaining 129 studies were judged as being at unclear risk due to insufficient information to determine randomisation methods. The majority of studies (n = 156) did not report allocation concealment and were judged as unclear. Fourteen studies were judged as being at low risk of bias as allocation was blinded. In 3 studies, the researchers were not blinded to the allocation process and we judged these studies as being at high risk of bias.

3.3.3.2 Performance and Detection Bias

All trials were at high risk of performance bias (i.e. blinding of participants to the intervention and outcomes). Lack of investigator blinding could have influenced measures of resting blood pressure and flow-mediated dilatation but is more likely to have had an impact on the motivation provided to participants during $\dot{V}O_2$Peak tests. The majority of studies (n = 144) were rated as unclear for detection bias (i.e. blinding of outcome assessor) due to insufficient information provided in the studies. Two studies were at high risk of detection bias, with the remaining 27 studies at low risk.

3.3.3.3 Attrition Bias

The majority (n = 122) of studies were judged as being at low risk for incomplete outcome data. A further 37 studies were rated as unclear risk due

to attrition rates > 20% in one of the study groups (i.e. control or RET). Few studies were rated as high risk (n = 14) due to high dropout rates or some participants being excluded from the analysis.

3.3.3.4 Reporting Bias

The majority (n = 166) of studies were rated as low risk for selective reporting bias. A further 4 studies were classed as unclear due to a lack of description of outcome measures and 3 studies rated as high risk as data for some outcomes were not reported.

3.3.3.5 Publication Bias

Funnel plots were produced for all outcomes, except flow-mediated dilatation (Appendix 2e). All funnel plots were asymmetrical, indicating publication bias.

3.3.4 Sensitivity Analysis

Results from the sensitivity analysis are summarised in Appendix 2f. Heterogeneity was reduced in 16/33 outcomes. The most considerable reductions were in those outcomes with fewer studies such as short-term systolic and diastolic blood pressure and long-term total and high-density lipoprotein cholesterol and these results could alter the main findings. However, in the outcomes with more studies (e.g. total cholesterol, high-density lipoprotein cholesterol) it is unlikely that this sensitivity analysis will alter the main findings.

3.3.5 GRADE Analysis

All outcomes were rated as very low or, low quality evidence demonstrating that the estimate of effect for those outcomes is uncertain (Table 4).

Table 4. GRADE summary of findings.

Outcome		Anticipated absolute effects (95% CI)		Number of participants (RCTs)	Certainty
		Risk with control group	Risk with resistance exercise training		
Cardiovascular morbidity/mortality		Could not be calculated due to lack of reporting.			
Systolic blood pressure (mmHg)	*ST*	**115.45** mmHg	MD **3.17 mmHg lower** (6.95 lower to 0.6 higher)	116 (4 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]
	MT	**122.8** mmHg	MD **4.02 mmHg lower** (5.92 lower to 2.11 lower)	1456 (46 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]
	LT	**131.6** mmHg	MD **4.88 mmHg lower** (10.55 lower to 0.78 higher)	346 (7 RCTs)	⨁⨁◯◯ LOW [a,c]
Mean arterial pressure (mmHg)	*ST*	**86.5** mmHg	MD **3.31 mmHg lower** (6.86 lower to 0.78 higher)	67 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]
	MT	**79.6** mmHg	MD **1.57 mmHg lower** (4.6 lower to 1.46 higher)	238 (10 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]
Diastolic blood pressure (mmHg)	*ST*	**65.2** mmHg	MD **1.44 mmHg lower** (4.73 lower to 1.86 higher)	52 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]
	MT	**74.3** mmHg	MD **1.73 mmHg lower** (2.88 lower to 0.57 lower)	1418 (45 RCTs)	⨁⨁◯◯ LOW [a,c]
	LT	**76** mmHg	MD **4.93 mmHg lower** (8.58 lower to 1.28 lower)	346 (7 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]
Resting heart rate (bpm)	*ST*	**72** bpm	MD **2.66 bpm lower** (7.55 lower to 2.23 higher)	30 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]
	MT	**67.8** bpm	MD **0.35 bpm higher** (1.44 lower to 2.13 higher)	977 (35 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]
	LT	**57.4** bpm	MD **0.48 bpm lower** (3.12 lower to 2.17 higher)	142 (5 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,e]
Flow Mediated Dilatation (%)		**7.8** %	MD **1.69 % higher** (0.97 higher to 2.41 higher)	138 (6 RCTs)	⨁⨁◯◯ LOW [a,c]
Total Cholesterol (mg/dL)	*ST*	**179.3** mg/dL	MD 5.55 **mg/dL lower** (9.62 lower to 5.47 higher)	146 (3 RCTs)	⨁◯◯◯ VERY LOW [a,c,e]
	MT	**180.9** mg/dL	MD **0.57 mg/dL higher** (5.63 lower to 6.77 higher)	882 (32 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]
	LT	**198.6** mg/dL	MD **8.71 mg/dL lower** (30.83 lower to 13.4 higher)	212 (8 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d,e]
High-density lipoprotein cholesterol (mg/dL)	*ST*	**53.8** mg/dL	MD **0.82 mg/dL higher** (5.4 lower to 7.03 higher)	146 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,e]
	MT	**53.3** mg/dL	MD **2.35 mg/dL higher** (0.66 lower to 5.35 higher)	1114 (38 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]
	LT	**53.5** mg/dL	MD **2.79 mg/dL higher** (0.69 lower to 6.82 higher)	339 (9 RCTs)	⨁⨁◯◯ LOW [a,c]
Low-density lipoprotein cholesterol (mg/dL)	*ST*	**105.6** mg/dL	MD **5.1 mg/dL lower** (11.09 lower to 0.9 higher)	146 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,e]
	MT	**110.1** mg/dL	MD **2.86 mg/dL lower** (8.77 lower to 3.05 higher)	1000 (31 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]
	LT	**118.3** mg/dL	MD **3.69 mg/dL lower** (10.99 lower to 3.6 higher)	265 (6 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]

Table 4 cont.

Triglycerides (mg/dL)	*ST*	**115.2** mg/dL	MD **3.63 mg/dL lower** (17.45 lower to 10.2 higher)	146 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,e]
	MT	**91.8** mg/dL	MD **3.99 mg/dL lower** (8.78 lower to 0.8 higher)	1165 (37 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]
	LT	**102.7** mg/dL	MD **2.82 mg/dL lower** (14.98 lower to 9.33 higher)	265 (6 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]
Fasted insulin (µU/ml)	*MT*	**16.2** µU/ml	MD **1.11 µU/ml lower** (1.74 lower to 0.49 lower)	590 (20 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]
	LT	**13.8** µU/ml	MD **0.4 µU/ml lower** (1.62 lower to 0.81 higher)	179 (4 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]
HOMA-IR	*MT*	**6.1**	MD **1.22 lower** (2.29 lower to 0.15 lower)	184 (9 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]
	LT	**3.8**	MD **0.18 lower** (0.64 lower to 0.27 higher)	71 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]
Fasted glucose (mg/dL)	*ST*	**87.3** mg/dL	MD **3.39 mg/dL lower** (6.9 lower to 0.11 higher)	122 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]
	MT	**100.7** mg/dL	MD **2.39 mg/dL lower** (4.47 lower to 0.31 lower)	984 (34 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]
	LT	**92.3** mg/dL	MD **0.7 mg/dL lower** (2.8 lower to 2.67 higher)	271 (7 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]
C-reactive protein (mg/L)	*ST*	**2.4** mg/L	MD **0.13 mg/L lower** (0.25 lower to 0.01 lower)	82 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,e]
	MT	**3.2** mg/L	MD **0.11 mg/L lower** (0.6 lower to 0.38 higher)	394 (12 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]
$\dot{V}O_2$Peak (ml/kg/min)	*ST*	**28.6** ml/kg/min	MD **2.07 ml/kg/min higher** (0.75 higher to 3.39 higher)	308 (9 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]
	MT	**28.9** ml/kg/min	MD **1.07 ml/kg/min higher** (0.38 higher to 1.76 higher)	1454 (48 RCTs)	⨁◯◯◯ VERY LOW [a,c,d,e]
	LT	**23** ml/kg/min	MD **1.22 ml/kg/min higher** (0.44 higher to 2.0 higher)	399 (11 RCTs)	⨁◯◯◯ VERY LOW [a,c,e]

CI - Confidence interval; RCTs – randomised controlled trials; MD – mean difference; ST – short term; MT – medium term; LT – long term; $\dot{V}O_2$Peak – peak rate of oxygen consumption.
a – Downgraded due to being a surrogate outcome.
b – Downgraded due to potential for a recommendation or clinical course of action differing if the upper versus the lower boundary of the CI represented the truth and/or a sample size < 400.
c – Publication bias suspected after inspection of funnel plots.
d – Inconsistent due to high heterogeneity, non-overlap of CI and/or markedly dissimilar point estimates.
e – Risk of bias was judged to be high.

3.3.6 Outcomes

A summary of the change observed for each outcome at all durations is presented as mean difference and 95% CI in Figure 6.

3.3.6.1 All-cause Mortality and Cardiovascular Events

None of the included studies reported on cardiovascular mortality, all-cause mortality, non-fatal endpoints such as myocardial infarction, CABG, PTCA, angina or angiographically-defined coronary heart disease, stroke, carotid endarterectomy or peripheral arterial disease.

Forest plots for each individual outcome are available in the supplementary documents (Appendix 2g). A summary of the change observed for each outcome at all time points is presented as mean difference and 95% CI in Figure 6.

3.3.6.2 Blood Pressure, Mean Arterial Pressure and Heart Rate

The effect of resistance training on systolic (SBP) and diastolic blood pressure (DBP) was investigated in 58 and 56 studies, respectively. Four studies investigated the effects of short-term resistance training on SBP (resistance arm n = 59, control arm n = 57). Figure 6 demonstrates a non-significant reduction in SBP following short-term resistance training interventions (mean diff, [95% CI]; -3.17 [-6.95, 0.6] mmHg $P = 0.1$; $\chi^2 = 5.76$, $I^2 = 48\%$, $P = 0.12$). Medium-term SBP included 46 studies (resistance arm n = 742, control arm n = 714) and demonstrated a significant reduction and considerable heterogeneity in SBP following medium-term resistance training interventions (-4.02 [-5.92, -2.11] mmHg, $P < 0.0001$; $\chi^2 = 325.48$, $I^2 = 86\%$, $P < 0.00001$). Long-term SBP included 8 studies (resistance arm n = 188, control arm n = 178) and showed a significant reduction favouring resistance training and substantial heterogeneity (-5.08 [-10.04, -0.13] mmHg, $P = 0.04$; $\chi^2 = 19.46$, $I^2 = 64\%$, $P = 0.007$).

Four studies investigated the effects of resistance training on short-term DBP (resistance arm n = 59, control arm n = 57). Figure 6 demonstrates a non-significant reduction in DBP following short-term resistance training interventions (-0.72 [-3.66, 2.22] mmHg $P = 0.63$; $\chi^2 = 8.1$, $I^2 = 63\%$, $P = 0.04$). Medium-term DBP included 45 studies (resistance arm n = 721, control arm n = 697) and revealed a significant reduction in DBP (-1.73 [-2.88, -0.57] mmHg, $P = 0.003$; $\chi^2 = 263.07$, $I^2 = 83\%$, $P < 0.00001$). Long-term DBP included 7 studies (resistance arm n = 177, control arm n = 169) and demonstrated a significant reduction favouring resistance training and considerable heterogeneity (-4.93 [-8.58, -1.28] mmHg, $P = 0.008$; $\chi^2 = 22.07$, $I^2 = 73\%$, $P < 0.001$; Figure 6).

MAP was reported in 13 studies. Three studies investigated the effects of short-term resistance training on MAP (resistance arm n = 35, control arm n = 32) with Figure 6 demonstrating a non-significant reduction (-3.31 [-6.86, 0.25] mmHg, $P = 0.07$; $\chi^2 = 6.61$, $I^2 = 70\%$, $P = 0.04$). Medium-term MAP included 10 studies (resistance arm n = 136, control arm n = 132) and demonstrated non-significant reduction in MAP over the course of a medium-term resistance training intervention (-1.57 [-4.6, 1.46], $P = 0.31$; $\chi^2 = 97.16$, $I^2 = 91\%$, $P < 0.00001$).

The effect of resistance training on resting heart rate was reported in 42 studies. Studies (n = 2) investigating the effects of resistance training on short-term resting heart rate (resistance arm n = 16, control arm n = 14) demonstrate no significant change (-2.66 [-7.55, 2.23] bpm, $P = 0.7$; $\chi^2 = 6.95$, $I^2 = 86\%$, $P = 0.008$; Figure 6). Medium-term resting heart rate included 35 studies (resistance arm n = 510, control arm n = 467) and Figure 6 shows no significant evidence of a change in resting heart rate over the course of a medium-term resistance training intervention (0.35 [-1.44, 2.13] bpm, $P = 0.69$; $\chi^2 = 266.11$, $I^2 = 87\%$, $P < 0.00001$). Long-term resting heart rate included 5 studies (resistance arm n = 74, control arm n = 68) and shows no evidence of change in long-term interventions (-0.48 [-3.12, 2.17] bpm, $P = 0.72$; $\chi^2 = 6.83$, $I^2 = 41\%$, $P = 0.15$).

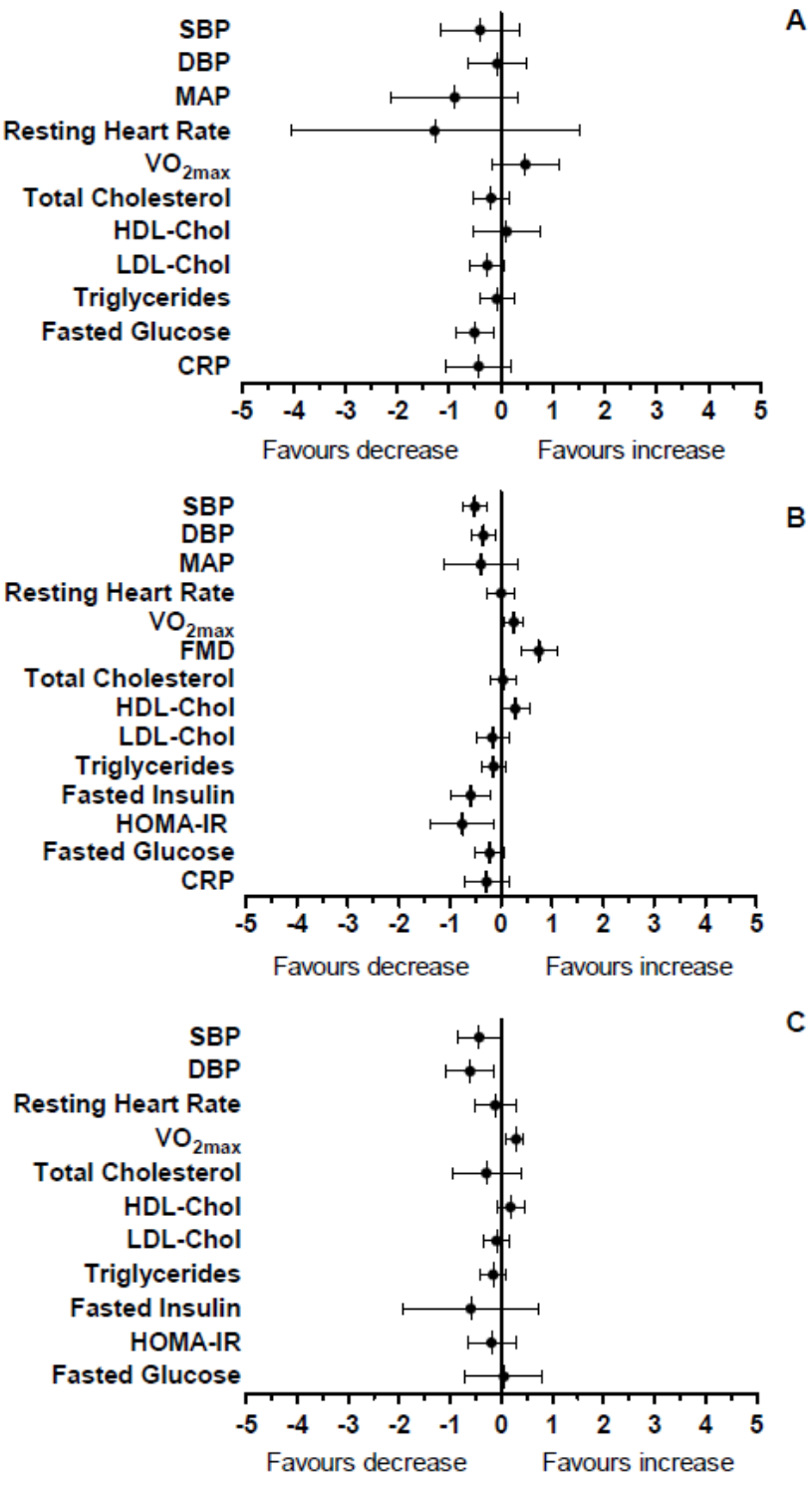

Figure 6. Effects of (A) Short-term, (B) medium-term, (C) long-term RET as standardised mean difference and 95% CI. SBP –systolic blood pressure, DBP - diastolic blood pressure, MAP – mean arterial pressure, $\dot{V}O_2$Peak – peak rate of oxygen consumption, FMD – flow mediated dilatation, HDL-Chol – high density lipoprotein cholesterol, LDL-Chol – low density lipoprotein cholesterol, HOMA-IR – insulin resistance, CRP – c-reactive protein.

3.3.6.3 $\dot{V}O_2$Peak

The effect of RET on $\dot{V}O_2$Peak is presented in Appendix 2g. There was an improvement in $\dot{V}O_2$Peak with RET and moderate heterogeneity (mean difference 2.07 [95% confidence interval 0.75, 3.39] ml/kg/min, *P* = 0.002; χ^2 = 11.35, I^2 = 30%, *P* = 0.18) in short-term studies (n=9; resistance arm: n = 177; control arm: n =131). In medium-term studies (n = 48; resistance arm: n = 767; control arm: n = 687) there was a significant improvement in $\dot{V}O_2$Peak with RET and substantial heterogeneity (mean difference 1.07 [95% confidence interval 0.38, 1.76] ml/kg/min, *P* = 0.002; χ^2 = 160.15, I^2 = 71%, *P* < 0.00001). In long-term studies (n = 11; resistance arm: n = 213; control arm: n = 186) there was a significant improvement in $\dot{V}O_2$Peak with RET (mean difference 1.22 [95% confidence interval 0.44, 2.0] ml/kg/min, *P* = 0.002; χ^2 = 10.22, I^2 = 2%, *P* = 0.42).

3.3.6.4 Flow-Mediated Dilatation

Eight studies reported flow-mediated dilatation, however due to missing data, only six studies (resistance arm: n = 68; control arm: n = 70), all medium-term, were included in the meta-analysis (Appendix 2g). There was a significant improvement in flow-mediated dilatation favouring RET (1.69 [0.97, 2.41], *P* < 0.0001) with low heterogeneity (χ^2 = 0.72, I^2 = 0%, *P* = 0.98). One short-term study (Olson, Dengel, Leon, & Schmitz, 2006) and one long-term study (Vona et al., 2009) reported improvements in flow-mediated dilatation after RET.

3.3.6.5 Blood Borne Biomarkers

All blood outcomes are presented in Table 5 and Appendix 2g. Non-significant changes in total cholesterol are evident at all durations (short: -5.55 [-16.58, 5.48], *P* = 0.32; medium: 0.57 [-5.63, 6.77], *P* = 0.86; long: -8.71 [-30.83, 13.40], *P* = 0.44). Non-significant, but favourable changes were also evident in medium- and long-term HDL-chol and across all intervention durations for LDL-chiol and triglycerides. Significant reductions in fasted insulin and HOMA-

IR was apparent in medium-term (-0.59 [-0.97, -0.21], *P* = 0.002 and -1.22 [-2.29, -0.15], *P* = 0.02, respectively) but not long-term interventions. There was a significant reduction in fasted glucose in medium-term (-2.39 [-4.47, -0.31], *P* = 0.02) but not short- or long-term interventions. There was significant heterogeneity in the CRP analysis; however, reductions of borderline statistical significance after medium- and long-term RET interventions were present.

3.3.7 Sub-group Analysis

All data for the sub-groups are available in Appendix 2h.

When comparing healthy young adults ≤ 40 years (n = 44) with healthy older adults ≥ 41 years (n = 50), there was a greater magnitude of cardiometabolic benefit from RET in the older populations. There were significant reductions in systolic blood pressure with medium-term RET interventions for healthy older adults compared to healthy younger adults (-4.36 [-5.73, -2.99] mmHg, *P* < 0.00001, versus -0.56 [-1.57, 0.44] mmHg, *P* = 0.27, respectively). In the healthy older adults there were significant improvements in systolic blood pressure, diastolic blood pressure, mean arterial pressure, resting heart rate, total cholesterol, high-density lipoprotein cholesterol, triglycerides, fasted insulin, fasted glucose and C-reactive protein following medium-term interventions compared to younger adults for the same intervention duration. Significant improvements after long-term interventions were also apparent for diastolic blood pressure, $\dot{V}O_2$Peak, total cholesterol and fasted glucose in healthy older adults ≥ 41 years compared to younger adults.

There were greatest improvements in medium-term LDL cholesterol, short- and medium-term $\dot{V}O_2$Peak, and short-term systolic and diastolic blood pressure among older adults (≥ 41 years) with elevated cardiometabolic risk or cardiometabolic disease (n = 42) after medium-term interventions, compared to healthy older adults. For example, the largest reduction in systolic blood pressure following medium-term RET interventions was observed in older adults ≥ 41 years with elevated cardiometabolic risk or disease (-8.80 [-

9.90, -7.69] mmHg, $P < 0.00001$) compared to the healthy older adults (-4.36 [-5.73, -2.99] mmHg, $P < 0.00001$).

Table 5. The short- (ST), medium- (MT) and long-term (LT) effects of resistance training on blood borne biomarkers

Blood marker		Number of studies	Number of participants		Mean difference [95% CI]	P values	Heterogeneity
			RT	CON			
Total Cholesterol (mg/dL)	*ST*	3	80	66	-5.55 [-16.58, 5.48] †	0.32	$\chi^2 = 2.39$, $I^2 = 16\%$, P = 0.3
	MT	32	442	440	0.57 [-5.63, 6.77]	0.86	$\chi^2 = 190.82$, $I^2 = 84\%$, P < 0.00001
	LT	8	115	97	-8.71 [-30.83, 13.40] †	0.44	$\chi^2 = 71.91$, $I^2 = 90\%$, P < 0.00001
HDL-chol (mg/dL)	*ST*	3	80	66	0.82 [-5.40, 7.03]	0.56	$\chi^2 = 5.99$, $I^2 = 50\%$, P = 0.11
	MT	39	601	590	2.23 [-0.06, 4.51] †	0.06	$\chi^2 = 734.44$, $I^2 = 95\%$, P < 0.00001
	LT	9	179	160	2.79 [-0.69, 6.28] †	0.12	$\chi^2 = 12.33$, $I^2 = 35\%$, P = 0.14
LDL-chol (mg/dL)	*ST*	3	80	66	-5.10 [-11.09, 0.90] †	0.1	$\chi^2 = 0.32$, $I^2 = 0\%$, P = 0.85
	MT	31	503	497	-2.86 [-8.77, 3.05] †	0.34	$\chi^2 = 292.46$, $I^2 = 90\%$, P < 0.00001
	LT	6	135	130	-3.69 [-10.99, 3.60] †	0.32	$\chi^2 = 2.39$, $I^2 = 0\%$, P = 0.79
Triglycerides (mg/dL)	*ST*	3	80	66	-3.63 [-17.45, 10.2] †	0.61	$\chi^2 = 0.14$, $I^2 = 0\%$, P = 0.93
	MT	37	590	575	-3.99 [-8.78, 0.8] †	0.29	$\chi^2 = 250.54$, $I^2 = 86\%$, P < 0.00001
	LT	6	135	130	-2.82 [-14.98, 9.33] †	0.65	$\chi^2 = 7.99$, $I^2 = 37\%$, P = 0.16
Fasted insulin (µU/ml)	*MT*	20	304	286	-0.59 [-0.97, -0.21] †	0.002*	$\chi^2 = 84.86$, $I^2 = 78\%$, P < 0.00001
	LT	4	89	90	-0.60 [-1.93, 0.72] †	0.37	$\chi^2 = 45.43$, $I^2 = 93\%$, P < 0.00001
HOMA-IR	*MT*	9	96	88	-1.22 [-2.29, -0.15] †	0.02*	$\chi^2 = 94.62$, $I^2 = 92\%$, P < 0.00001
	LT	3	38	33	-0.18 [-0.64, 0.27] †	0.6	$\chi^2 = 1.45$, $I^2 = 0\%$, P = 0.48
Fasted glucose (mg/dL)	*ST*	2	64	58	-3.39 [-6.90, 0.11] †	0.06	$\chi^2 = 1.66$, $I^2 = 40\%$, P = 0.2
	MT	33	499	485	-2.39 [-4.47, -0.31] †	0.02*	$\chi^2 = 318.33$, $I^2 = 90\%$, P < 0.00001
	LT	7	135	136	-0.07 [-2.80, 2.67] †	0.96	$\chi^2 = 46.09$, $I^2 = 87\%$, P < 0.00001
CRP (mg/L)	ST	2	41	41	-0.43 [-1.05, 0.19] †	0.07	$\chi^2 = 1.58$, $I^2 = 37\%$, P = 0.21
	MT	12	199	195	-0.28 [-0.72, 0.15] †	0.20	$\chi^2 = 44.57$, $I^2 = 75\%$, P < 0.00001

* Indicates statistical significance. † Indicates favouring resistance training. ST – short term, MT – medium term, LT – long term, HDL-chol – high density lipoprotein cholesterol, LDL-chol – low density lipoprotein cholesterol, HOMA-IR – insulin resistance, CRP – C-reactive protein.

3.3.8 Adverse Events

One hundred and twenty-three RCTs (71%) did not report the occurrence of adverse events. Fifty studies (29%) reported information on adverse events and 17 of these reported that no adverse events occurred. Of the 50 studies reporting adverse events, 16 studies reported more than one adverse event occurring. Musculoskeletal injuries (e.g. lower back pain, knee pain) as a result of the intervention were reported in 20 studies (n = 20/50; 40%), with more than one adverse event being reported in 15 of the 20 studies. Two studies (4%) detailed discomfort and muscle soreness related to RET. Illness or injury unrelated to RET were reported in seven (14%) studies. Three studies (6%) reported that participants suffered injuries but the details and whether they were related to the intervention, was unclear. Syncope, possibly related to the intervention, was reported in three studies (6%). Cardiac issues (e.g. myocardial infarction, angina) thought to be unrelated to the RET were reported in four (8%) studies. Respiratory problems, unrelated to the intervention, were reported in two (4%) and hypoglycaemia in a further two (4%) studies. Four studies (8%) identified participants who underwent elective surgery unrelated to the study. Five studies (10%) reported a newly diagnosed condition or change in medication. Other adverse events reported only once included death (car crash), cerebral stroke, abdominal hernia and deep vein thrombosis; these were not associated with RET. Personal or professional issues resulting in withdrawal from the programme were reported in 5 (10%) studies.

3.4 Discussion

3.4.1 Summary of Evidence

Resistance exercise training had a positive impact on cardiometabolic health, via improvements in resting blood pressure, $\dot{V}O_2$Peak and blood biomarkers of cardiometabolic risk. These improvements were most convincing for medium-term (7-23 weeks) interventions, which is likely to reflect the higher volume of published studies compared to short- (< 6 weeks) and long-term (≥

24 weeks) intervention durations. Relatively few studies have primarily investigated the cardiometabolic health benefits of RET in clinical populations, particularly those at elevated risk of cardiovascular events. There is limited evidence of adverse events associated with RET with only 12% of studies included in the review reporting musculoskeletal injuries. Other studies reported transient levels of muscle soreness following RET, which is common after unaccustomed muscular exercise (Cheung, Hume, & Maxwell, 2003; McHugh, 2003; Nosaka, Sakamoto, Newton, & Sacco, 2001). Therefore, we suggest that RET is a safe exercise option for both healthy and clinical populations.

There was a positive effect of RET on systolic and diastolic blood pressure. The reductions observed are of similar magnitude to those after aerobic exercise interventions (Arora, Shenoy, & Sandhu, 2009; Collier et al., 2009; Fenkci, Sarsan, Rota, & Ardic, 2006; Yavari, 2012), and could suggest a dose-response relationship for interventions of varying durations. Furthermore, given that hypertension is a global cause of mortality (World Health Organisation, 2009), the pronounced effects of RET on blood pressure outcomes in older populations observed in our subgroup analyses suggest that RET could be an effective non-pharmacological strategy for the prevention and/or control of hypertension in older adults who are at elevated cardiometabolic risk.

The effect of RET on mean arterial pressure and resting heart rate was not statistically significant. Although resting heart rate may be less sensitive to change after RET, the lack of effect on mean arterial pressure (particularly for medium-term studies) could be due to few studies reporting mean arterial pressure in comparison to systolic or diastolic blood pressure. Additionally, diastolic blood pressure has a greater influence on mean arterial pressure than systolic blood pressure and, due to the less pronounced effect of RET on diastolic blood pressure, this could have impacted upon the significance of mean arterial pressure.

Low cardiopulmonary fitness has an indirect effect on cardiovascular disease risk and is partially (40-60%) mediated by cardiovascular risk factors including

hypertension, hypercholesterolemia, obesity and fasting glucose (Erez, 2015). Therefore, the beneficial effects of RET on $\dot{V}O_2$Peak is important. Traditionally, RET has not been used to provide a stimulus for improving cardiopulmonary exercise capacity, however our findings suggest that RET may be a reasonable choice for improving this health outcome. Improvements in $\dot{V}O_2$Peak after RET were modest (short-term: 2.38 [0.76, 4.00] ml/kg/min; medium-term: 1.13 [0.50, 1.76] ml/kg/min; long-term: 1.23 [0.6, 1.87] ml/kg/min). However, larger effects were observed for older adults at elevated cardiometabolic risk. This is clinically important since it suggests that RET may contribute to reducing the risk of cardiovascular morbidity and mortality in high risk populations (Kavanagh et al., 2003). On the other hand, it is also possible that those who participated in RET also increased their participation in aerobic activity. Exercise training outside of RET interventions was generally not monitored and may account for some of the change in $\dot{V}O_2$Peak after RET.

Endothelial dysfunction is associated with cardiovascular disease and the ageing process. Endothelial dysfunction is linked to a decrease in nitric oxide availability, which can be improved through exercise (Seals, 2011). A deterioration in flow-mediated dilatation of approximately 1% is associated with a 13% increased risk of future cardiovascular events (D. J. Green, Jones, Thijssen, Cable, & Atkinson, 2011; Inaba et al., 2010). We found improvements in endothelial function (flow-mediated dilatation) with RET programmes that lasted 7-23 weeks. This is likely to result from shear stress-induced adaptations in nitric oxide metabolism resulting from muscular contractions, resting heart rate and blood pressure changes during RET (Vona et al., 2009). Shear-stress induced adaptations may not be restricted to blood vessels within the active skeletal muscles, as exercise programmes that are performed predominantly with the legs induce improvements in brachial artery flow-mediated dilatation (Birk et al., 2012). Therefore, RET may be an effective stimulus for improving flow-mediated dilatation, potentially reducing the risk of cardiometabolic disease.

The most favourable changes in blood biomarkers were apparent in short- and medium-term studies in the pooled analysis. The lower number of longer-term studies may have reduced the level of statistical power required to detect

significant changes. We found greater reductions in low-density lipoprotein cholesterol, triglycerides and fasted glucose among older adults. There were also significant reductions in C-reactive protein after short- and medium-term RET among older adults at elevated cardiometabolic risk (Table 5 and Supplementary Table 7). Reductions in C-reactive protein, fasted glucose and insulin, and HOMA-IR could have been mediated by the effect of RET on body composition, including an increase in skeletal muscle mass and reduction in fat mass, and the resulting impact on adipokine secretion (De Salles, 2010; Libardi, De Souza, Cavaglieri, Madruga, & Chacon-Mikahil, 2012), insulin sensitivity (Sañudo et al., 2013) and glucose transport (Azarbayjani et al., 2014; Williams, 2007). These improvements in metabolic functioning following RET could have important clinical implications for the prevention and treatment of metabolic syndrome, type 2 diabetes mellitus and cardiovascular disease (Donges, Duffield, & Drinkwater, 2010; Fenkci et al., 2006; Libardi et al., 2012; Wojtaszewski, 2006).

Future studies on RET interventions should monitor or control for the potential confounding influence of aerobic exercise outside of the intervention. It is unclear whether improvements in $\dot{V}O_2$Peak after RET are more attributable to the cardiopulmonary stimulus of RET leading to improved oxygen transport (via increased cardiac stroke volume) or metabolic adaptations resulting in improved utilisation of oxygen at the level of skeletal muscle. Improvements in $\dot{V}O_2$Peak following medium- to long-term programmes of aerobic exercise training tend to be greater and mainly reflect an increase in cardiac stroke volume in previously untrained individuals (O'Connor et al., 2017; Saltin et al., 1968). The relative importance of, and potential to maximise central, systemic and peripheral adaptations, by altering the characteristics of RET (e.g. sets, repetitions, rest etc.) warrants further research. Furthermore, additional high-quality research is also required to formulate the optimal design of a RET programme to promote cardiovascular health and risk factor management in middle-aged and clinical populations.

3.4.2 Limitations

The main findings of this systematic review need to be considered in the context of some key limitations, including restricting the search to two electronic databases, language bias and unexplained statistical heterogeneity for some of the analyses. Publication bias was also evident, and is probably attributable to inadequate data analysis, poor methodological quality and/or varying sample sizes of included studies. It is unlikely that selective outcome reporting influenced the funnel plots as 90.6% of the studies were rated as low risk for this outcome. Additionally, poor methodological quality of some of the included studies could have affected the estimates of the outcomes. Although all the included studies were RCTs, few studies adequately reported the randomisation process (n = 36), allocation concealment (n = 14), or blinding of outcome assessment (n = 27). Therefore, many studies were rated as unclear bias in multiple categories, and this may have contributed to the lack of reduction in heterogeneity in the sensitivity analyses. Additionally, some data were not pooled due to lack of access to the mean (SD) scores.

Reporting must improve, as many studies had incomplete descriptions of RET programmes and progression, small sample sizes, inadequate documentation of adherence and lacked detail regarding the timing of blood sampling in relation to the last bout of exercise (potentially influencing circulating levels of blood biomarkers). Improved reporting of trials may also improve the quality of evidence, as all outcomes in this review were graded as either very low or low quality, and higher-quality reporting of outcomes may alter the effect estimates. Authors should follow guidelines when reporting trials such as the TIDieR checklist and guide (Hoffmann et al., 2014).

Studies of varying duration are needed, as the majority included in our systematic review involved medium-term interventions. In addition, data analyses were often based only on participants who successfully completed the training intervention, rather than applying an intention to treat analysis. This could have altered the study results (Akl et al., 2012; S. P. T. Higgins, & Green, S., 2011). Finally, cardiorespiratory fitness levels of participants prior to a RET

intervention is likely to influence training-induced adaptations and this should be considered in future research.

3.5 Conclusions

This systematic review provides quantitative estimates of the effects of RET on indices of cardiometabolic health in adults. RET appears a safe mode of exercise in both healthy and clinical populations and effective for inducing improvements in resting blood pressure, FMD, HOMA-IR, fasted glucose and insulin. There are also improvements in $\dot{V}O_2$Peak, which are less pronounced than those reported after programmes of aerobic exercise training. Future studies should aim to provide a detailed overview of the RET programme and progression methods in order for the optimal design of a RET programme for optimising improvements in cardiometabolic health to be explored. In addition, future research should investigate the effects of RET on cardiovascular health and risk factor management in healthy older and older clinical populations (> 50 years of age) both in a supervised and home-based setting and include long-term clinical end-points.

CHAPTER 4

CROSS-SECTIONAL STUDY OF PATIENT-REPORTED FATIGUE, PHYSICAL ACTIVITY AND CARDIOVASCULAR STATUS IN MEN AFTER ROBOTIC-ASSISTED RADICAL PROSTATECTOMY

4.0 Cross-sectional study of patient-reported fatigue, physical activity and cardiovascular status in men after robotic-assisted radical prostatectomy

4.1 Introduction

Radical prostatectomy is an accepted curative treatment option for men with clinically localised significant prostate cancer with greater than 10 years life expectancy and the ability to perform activities of daily living (National Institute for Health and Care Excellence, 2014b). Robotic-assisted radical prostatectomy is now the most prevalent modality for surgical removal of the prostate for prostate cancer in the UK (Khadhouri et al., 2018).

Robot-assisted radical prostatectomy has been demonstrated to be associated with lower blood loss and decreased hospital stay when compared to open radical prostatectomy (Djavan et al., 2010). Although commonly assumed that men undergoing radical prostatectomy are fit and return to their pre-operative physical activity levels after surgery, there is little published data to substantiate this assumption. Additionally, few studies performed to date have explored cancer-related fatigue after robot-assisted radical prostatectomy. The limited data suggests that fatigue, which is often limited by treatment modality, is evident in prostate cancer patients and it has previously been reported that approximately 14% of patients who have undergone radical prostatectomy experience fatigue (Köhler et al., 2014; Storey et al., 2012). Therefore, the prevalence of fatigue and post-operative physical fitness in men who have undergone robot-assisted radical prostatectomy is largely unknown. Fatigue in cancer patients and survivors has been associated with reduced physical activity levels (Blaney, Lowe-Strong, Rankin-Watt, Campbell, & Gracey, 2013), potentially adversely affecting cardiovascular risk profile and recovery to full functional fitness after robot-assisted radical prostatectomy.

To our knowledge, no study has explored the association between self-reported physical activity, fatigue and comorbidities in men who have undergone robot-assisted radical prostatectomy. The aim of this pilot study

was to characterise fatigue, physical activity levels and cardiovascular status, over a two-week period, in men after robot-assisted radical prostatectomy and compare this with those on ADT to establish whether this is a substantial problem which future intervention studies should address.

4.2 Methods

4.2.1 Design

A cross-sectional questionnaire study was administered to men who had undergone robot-assisted radical prostatectomy and men treated with ADT for prostate cancer. Ethics approval was granted by Northumbria University Ethics Committee. Approval was then obtained (ref: 202404) from the Health Research Authority (Appendix 1a). Ethics approval from NHS REC South Scotland was obtained on 8th September 2016 (ref: 16/SS/0143; Appendix 1b) and further approved by NUTH Research and Development on 11th October 2016 (ref: 7832; Appendix 1c). The study was conducted according to the Helsinki Declaration (1964; revised 2001). Data from the ADT cohort of men is presented as a comparative control population.

This study was conducted at Newcastle upon Tyne Hospitals NHS Foundation Trust which is a tertiary referral centre serving a population of 1.2 million people. Robot-assisted radical prostatectomy was performed by three experienced surgeons at the institution over the study period.

4.2.2 Participants

Men were eligible to participate in the study if they: (1) had histologically confirmed prostate cancer; (2) were at least 8 weeks after their treatment for prostate cancer with either robot-assisted radical prostatectomy or after initiation of ADT, and; (3) were able to provide consent and satisfactorily complete written questionnaires. All eligible patients attending outpatient clinics were approached. Men receiving any other treatment for prostate cancer were excluded from the study.

4.2.3 Study Outcome Data

Consenting men were asked to provide demographic information including current health status via a questionnaire, average weekly alcohol intake and smoking status. Stature and body mass were measured. They were then invited to complete a questionnaire booklet containing validated questionnaires prospectively over a two-week period (see further details below) and return the booklet in a prepaid stamp addressed envelope. Questionnaire score calculations were performed in accordance with published questionnaire protocols. Likewise, missing data were treated in accordance with the questionnaire protocols. The questionnaires included are detailed below.

4.2.3.1 Comorbidity and Cardiovascular Status

Charlson Comorbidity Index was calculated using information provided on stature, body mass and information from patients medical records (Charlson, Pompei, Ales, & MacKenzie, 1987; MDCalc, 2018). The risk of suffering a heart attack or stroke within the next 10 years was calculated using Q-Risk2 (Hippisley-Cox et al., 2008). Q-Risk2 score is calculated from patient-reported family history and smoking status, along with information from the patients' medical records such as age, gender, ethnicity, and selected physiological measurements (e.g. diabetes, angina, atrial fibrillation, blood pressure, cholesterol levels). Q-Risk 2 can be categorised as < 10% (low), 10-20% (medium) or > 20% (high) (Coghill, Garside, Montgomery, Feder, & Horwood, 2018).

4.2.3.2 Scottish Physical Activity Questionnaire

The Scottish Physical Activity Questionnaire (SPAQ) was completed at the end of both weeks as a recall questionnaire and has good reliability (Cronbach's alpha = 0.998) (Lowther, Mutrie, Loughlan, & McFarlane, 1999). This questionnaire assesses moderate to vigorous physical activity (MVPA) over

the previous 7 days. The questionnaire includes sections for both leisure time and occupational physical activity with each section containing questions on general activity such as walking, stair climbing and manual labour (Lowther et al., 1999). The average weekly total MVPA (mins) was calculated in addition to the mean total for each individual exercise component.

4.2.3.3 Brief Fatigue Inventory

The Brief Fatigue Inventory (BFI) was completed at the end of each day for all 14 days of the data collection period to rapidly assess fatigue in cancer patients and is correlated with other validated fatigue questionnaires (Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003; Mendoza et al., 1999; Sternberg et al., 2013) and has good reliability (Cronbach's alpha = 0.95) (Mendoza et al., 1999). The BFI consists of three questions assessing fatigue severity and six questions assessing the interference of fatigue with the patient's mood and social/physical functioning with all answers being on a 0-10 scale. A global fatigue score was obtained for weeks 1 and 2 by averaging all the items on the BFI and as an average of the whole 2-week period (Mendoza et al., 1999). Clinically significant fatigue was defined as a global fatigue score > 3 (Shafqat et al., 2005; Storey et al., 2012).

4.2.3.4 Stage of Change Questionnaire

The Stage of Change Questionnaire was administered once at the start of the two-week study period to assess patient's attitudes towards exercise behaviour change and has acceptable reliability (Cronbach's alpha = 0.63) (R. J. Donovan, Jones, Holman, & Corti, 1998) . Participants answered 'yes' or 'no' to four statements to assess each individual's stage of behaviour change (Blaney et al., 2013). The stages are categorised as follows: stage 1 – pre-contemplation, stage 2 – contemplation, stage 3 – preparation, stage 4 - action and, stage 5 – maintenance.

4.2.4 Statistical Analysis

All returned surveys were included in the analysis, even if some sections were incomplete. Consequently, the number of total responses for each survey item varied because of missing data. Analyses were conducted using IBM SPSS Statistics Version 22 (IBM United Kingdom Limited, Hampshire, United Kingdom).

Normality was assessed using the Shapiro-Wilk test and if data was not normally distributed, transformations were conducted using common logarithms or square root. To assess the associations of the outcomes with self-reported total physical activity levels (SPAQ), Pearson correlations and Spearman's rank were employed. Independent samples t-tests were used to examine differences between the two treatment groups with $P < 0.05$ chosen as the accepted level of significance.

4.3 Results

4.3.1 Participants

In total, 148 men were approached to take part in the study and 96 men consented to participate in the study, of these 62/96 (65%) participants returned postal questionnaires. Table 6 illustrates the demographic of the cohort. The patients approached were on average 11.7 months after robot-assisted radical prostatectomy and 22.1 months after the initiation of ADT. The robot-assisted radical prostatectomy cohort comprised 42/62 responses, of these 57% and 14% were classified as overweight and obese respectively.

4.3.2 Cardiovascular Status

Charlson Comorbidity Index calculations indicated there was no significant difference in estimated 10-year survival after robot-assisted radical prostatectomy (87.3% ± 12.2%) or ADT (80.5% ± 18.7%), $t(27.2) = 1.5$, $P = 0.2$. Q-Risk2 scores indicated that there was no significant difference in 10

year risk of suffering a heart attack or stroke between men after radical prostatectomy (18.1% ± 7.4%) and after initiation of ADT (22.4% ± 10.8%), $t(28.4) = -1.6$, $P = 0.12$.

Table 6. Participant demographics.

	RARP (n = 42)	**ADT (n = 20)**
Age *(years)*	63.8 ± 6.4	67.3 ± 9.0
Body Mass *(kg)*	86.7 ± 13.4	86.4 ± 12.3
Stature *(cm)*	180 ± 0.07	176 ± 0.07
Body Mass Index *(kg/m^2)*	27.0 ± 3.9	27.8 ± 12.3
Drink Alcohol *n (%)*	38 (90.5)	18 (80.0)
Months since treatment *mean (range)*	11.7 (2-115)	22.1 (2-120)
Pre-RARP PSA	10.05 ± 6.3	
Pathological Gleason Score *(n)*		
GS 6	2	
GS 3 + 4	25	
GS 4+ 3	7	
GS ≥8	8	
Pathological Tumour Stage *(n)*		
PT2	24	
PT3a	13	
PT3b	5	

Data are presented as mean ± standard deviation unless stated otherwise. RARP – robot-assisted radical prostatectomy, ADT – androgen deprivation therapy, PSA – prostate specific androgen.

4.3.3 Physical Activity

The levels of reported total physical activity did not differ over the 2-week period between the two treatment groups (robot-assisted radical prostatectomy total average mins = 658.1 ± 337.6 verses ADT total average mins = 631.9 ± 318.5, $t(59) = 0.3$, $P = 0.8$). Age, body mass, BMI and BFI scores were not associated with the total amount of physical activity performed in either treatment group (Table 7). Approximately 50% of all physical activity

reported in both groups involved walking (e.g. walking to the shops/work, stair walking). Activities included in the 'other' category included yoga (1/42 post-radical prostatectomy, 1/20 ADT), bowls (1/42 post-radical prostatectomy) and rambling (2/42 post-radical prostatectomy, 1/20 ADT). A breakdown of the amount of physical activity undertaken is illustrated in Table 8.

Table 7. Correlation matrix between physical activity and demographic factors, stage of change and fatigue.

	Physical Activity[a]	
	RARP	**ADT**
Age	-0.1	-0.14
Body Mass	-0.02	-0.31
Body Mass Index	0.1	-0.09
Stage of Change	0.36 [b]	0.15
Brief Fatigue Inventory	-0.09	0.09

[a]Total physical activity in minutes averaged over the two-week study period.
[b] Spearman's Rank correlation is significant at the 0.05 level.
RARP - robot-assisted radical prostatectomy; ADT – androgen deprivation therapy

Table 8. Self-reported MVPA over the 2-week period.

	RARP	**ADT**
Total *(mins)*	658.1 ± 337.6	631.9 ± 318.5
Walking *(mins)*	341.4 ± 245.5	319.5 ± 251.4
Manual labour *(mins)*	125.4 ± 168.3	92.3 ± 158.2
Active housework *(mins)*	57.6 ± 79.6	82.4 ± 89.4
Dancing *(mins)*	3.2 ± 11.3	0.63 ± 2.8
Sport/Leisure activities *(mins)*	92.3 ± 178.5	126.4 ± 209.4
Other activities *(mins)*	40.4 ± 100.2	6.3 ± 22.3

Data are presented as mean ± standard deviation.
Two RARP participants did not provide physical activity data for week 1 or week 2.
RARP - robot-assisted radical prostatectomy; ADT – androgen deprivation therapy

4.3.4 Fatigue

All participants were experiencing fatigue over the two-week study period, the majority of fatigue reported was mild-moderate in severity and of borderline clinical significance. The mean severity of fatigue was significantly less over the two-week study period in the robot-assisted radical prostatectomy (1.6 ± 1.7) than in the ADT group (2.6 ± 1.8), $t(60) = -2.628$, $P = 0.011$ (Figure 7). In addition, 9/42 (21.4%) participants post-radical prostatectomy and, 6/20 (30%) ADT participants, reported clinically significant fatigue. There was no association between fatigue and the amount of self-reported physical activity (Table 7).

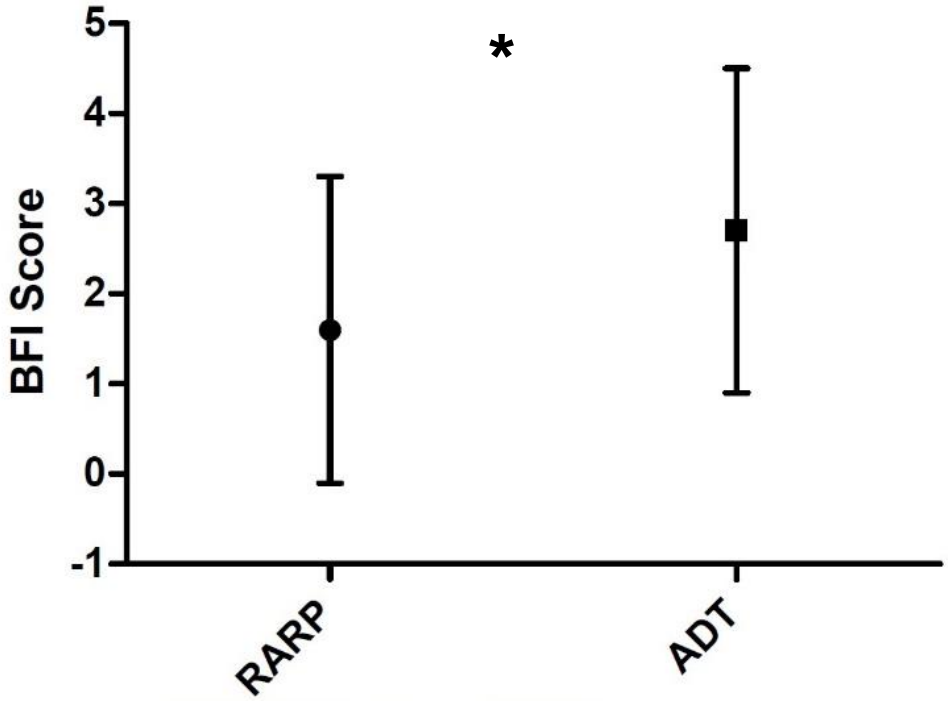

Figure 7. Reported fatigue severity over a 2-week period. RARP - robot-assisted radical prostatectomy; ADT – androgen deprivation therapy.
* represents statistical significance ($P < 0.05$)

4.3.5 Stage of Change

The majority of participants in both treatment groups reported being in the maintenance stage of change (Table 9). The maintenance phase is where individuals have made specific modifications to their exercise behaviour, however, it requires a conscious effort to maintain it. The stage of change outcomes positively correlated with the amount of physical activity undertaken in the robot-assisted radical prostatectomy treatment group, this is shown in Table 9.

Table 9. Stage of change scores for both treatment groups.

Stage of change (number of patients)	**RARP (n = 42)**	**ADT (n = 20)**
Stage 1 - Pre-contemplation	0	0
Stage 2 - Contemplation	1	3
Stage 3 - Preparation	0	1
Stage 4 - Action	5	3
Stage 5 - Maintenance	36	13
RARP - robot-assisted radical prostatectomy; ADT – androgen deprivation therapy.		

4.4 Discussion

This is the first study to our knowledge to quantitatively explore cardiovascular risk, fatigue and physical activity, in men who have undergone robot-assisted radical prostatectomy as a prostate cancer treatment. This study found that a significant proportion of men post-radical prostatectomy are at an increased risk of suffering a cardiovascular related event within 10-15 years of their surgery and > 20% may suffer from clinically significant fatigue. Importantly this study suggested that these findings were present in men appearing to meet the UK public health guidance of undertaking at least 150 minutes a week of moderate to vigorous aerobic physical activity.

The present study identified that the Q-Risk2 score of the robot-assisted radical prostatectomy cohort indicated that they were at an 18% risk of suffering a heart attack or stroke within the next 10 years. Whilst cardiovascular risk status has been studied extensively in patients receiving ADT (Gilbert, Tew, Bourke, Winter, & Rosario, 2013; Keating, 2017; Voog et al., 2016; Wallis et al., 2016), there are no studies as far as the authors are aware to date which have characterised the cardiovascular risk status of robot-assisted radical prostatectomy patients. The largest most contemporary study by Wilt et al. (2012), which gives a signal as to mortality risk from causes other than prostate cancer in a radical prostatectomy population. During a median follow-up period of 10 years, 171/281 of the radical prostatectomy group died and of these deaths 74% (127/171) were not due to prostate cancer (Wilt et al., 2012). Whilst it cannot be inferred that cardiovascular disease was the cause of all of these deaths due to other factors such as old age, this analysis combined with the findings from this study indicate potentially more can be done to improve the health of patients undergoing radical prostatectomy. The Q-Risk2 calculator predicts fatal and non-fatal cardiovascular disease, such as myocardial infarction, coronary heart disease, stroke and transient ischaemic attacks. The results of this study showed that our robot-assisted radical prostatectomy cohort were at a 3% elevated risk of cardiovascular disease when compared to moderately active males of a similar age (West, 2015). This finding, were it to be replicated in future larger-scale cohorts, supports the view that men after robot-assisted radical prostatectomy men should be offered lifestyle interventions to improve their cardiovascular health.

Cancer-related fatigue has previously been reported as a side effect of prostate cancer treatment in up to 80% of men (Luo et al., 2016; Segal et al., 2009; Stone et al., 2000; Taaffe et al., 2017). Few studies have investigated levels of fatigue in men who have exclusively undergone robot-assisted radical prostatectomy for prostate cancer however much work has been conducted in men receiving ADT and radiotherapy. Storey et al. (2012) performed a cross-sectional questionnaire study in 2005 of recurrence free survivors who had undergone open radical prostatectomy utilising the BFI. Clinically relevant fatigue was identified in 22% (29/133) of men undergoing radical

prostatectomy, whereas in their control non-cancer population the incidence of clinically relevant fatigue was 16% (10/63) at a median follow up of 56 months after treatment. Within their radical prostatectomy cohort median age 72, coexisting depression had the strongest independent association with fatigue. Storey et al. (2012) did not examine physical activity levels within their cohort. Cancer-related fatigue has been acknowledged to be debilitating and to significantly impact on quality of life (Berger et al., 2015). We have shown that after robot-assisted radical prostatectomy in a contemporary younger population, similar to Storey et al. clinically relevant fatigue is reported by 20% of men at a mean follow up of 11.7 months. This finding might be considered unexpected and highlights that post-treatment fatigue should be discussed with patients when they are counselled for robot-assisted radical prostatectomy. All patients included in this study underwent holistic needs assessment after treatment and received targeted support if required as part of routine care from a survivorship nurse specialist (J. J. Aning et al., 2018; Ferguson & Aning, 2015). It has previously been demonstrated that patients who undergo robot-assisted radical prostatectomy experience an unchanged overall quality of life (J. J. Aning et al., 2018). Therefore, it is possible that within our cohort the levels of clinically relevant fatigue identified are unlikely to result from psychological factors.

This study found patient reported levels of physical activity after robot-assisted radical prostatectomy which met current UK public health guidelines within the robot-assisted radical prostatectomy cohort despite a high proportion of our patients having a high body mass index. We demonstrated that physical activity levels did not correlate with fatigue levels in our cohort suggesting that fatigue levels may not be a barrier to the amount of physical activity undertaken within this population. Although public health guideline levels of aerobic physical activity were met, we identified that after robot-assisted radical prostatectomy, patients did not achieve the recommended weekly amount of resistance exercise (Department of Health, 2011). None of the patients who took part in this study reported completing any resistance-based exercise. This important finding highlights a potential area of unmet need in the post-radical prostatectomy population. Resistance exercise has previously been examined

in other prostate cancer treatment groups, both epidemiologically and during interventional studies which found resistance exercise to be safe in the population, it can assist in mitigating fatigue and generated longer-term improvements in quality of life, strength, triglycerides, and body fat when compared to aerobic exercise (Cormie et al., 2013; Segal et al., 2003; Segal et al., 2009). As far as we are aware, this is the first time an examination of physical activity sub-classifications has been undertaken in a contemporary population of men who have undergone robot-assisted radical prostatectomy. The potential benefits of resistance exercise in relation to cardiometabolic risk profile were highlighted in a recent meta-analysis (Ashton et al., 2018). Although loss of skeletal muscle mass has been widely reported in prostate cancer patients undergoing ADT (Galvao et al., 2009; Owen et al., 2017; Winters-Stone, Dieckmann, et al., 2015) and many studies have investigated the impact of resistance exercise training programmes (Hasenoehrl et al., 2015; Segal et al., 2003; Winters-Stone, Dieckmann, et al., 2015), much fewer studies have assessed changes in skeletal muscle characteristics after robot-assisted radical prostatectomy. There is a need for future research to address this evidence gap and extending the provision of structured exercise interventions (including resistance exercise) to this population may be warranted. Such interventions could have a positive impact on fatigue in men recovering from robot-assisted radical prostatectomy, as demonstrated previously in fatigued prostate cancer patients receiving ADT (Taaffe et al., 2017).

This study's findings add quantitative depth to recent qualitative work performed by Sutton et al. (2017) and Hackshaw-McGeagh et al. (2017) identifying patients' priorities. These studies showed that men undergoing robot-assisted radical prostatectomy would value physical activity and dietary advice from their healthcare professional and would prefer to receive this at an early stage. In addition, they provided evidence that men undergoing robot-assisted radical prostatectomy are willing to change their behaviour to improve their health, but they wish to be supported by their healthcare professional team to do so. The cohort of men in this study reported being in the maintenance phase derived from the stage of change questionnaire. This

demonstrates that they are aware that they are physically active and do not believe that they should be altering their current exercise regime. However, it is evident from the SPAQ that all patients within this cohort do not meet the UK guidelines for resistance-based exercise. Undergoing radical prostatectomy is potentially a 'teachable moment' to change exercise behaviour and we have demonstrated that this population is at risk of both cardiovascular events and fatigue. Qualitative research shows men are receptive to health behaviour change (Er et al., 2017; Hackshaw-McGeagh et al., 2017; Sutton et al., 2017) and such initiatives targeted at this population could have much potential to improve men's overall health. This study supports consideration of further targeted research into strategies aimed at improving the health of men who have undergone robot-assisted radical prostatectomy. Feasibility to recruit patients and compliance with completing study questionnaires has been demonstrated, in addition to the ability to discriminate the health status and behaviours of the robot-assisted radical prostatectomy population.

4.4.1 Limitations

The present study has limitations. Whilst the patient reported questionnaire data showed that men appeared to meet UK guidance for aerobic physical activity levels, it is possible that poor accuracy of self-reported physical activity lead to an overestimation of the total amount and therefore there may be an opportunity to use activity trackers in parallel to the questionnaires to verify the findings of future studies. Additionally, the SPAQ does not allow for the separation of exercise at varying intensities and therefore potential over reporting of the amount of MVPA may have occured. For example, within the walking category some low-intensity physical activity may have been included despite the instructions stating otherwise. We believe that our findings would justify the inclusion of activity trackers used in parallel with patient-reported activity questionnaires in future study protocols to strengthen validity of such activity outcome results. The numbers included in this study were small meaning caution is needed when interpreting the results. However, this study

has identified the need for further research in this population of men and informed the sample size calculation required for further work in this area. In order to conduct a fully powered study using the reported fatigue effect size from this pilot study (Cohen's *d* = 0.57) the minimum total sample size to achieve 80% power (α = 0.05) was determined as n = 100 patients (50 patients in each group). This would allow more precise estimates of fatigue prevalence as well as cardiometabolic risk and physical activity levels between the two groups to be detected (Cohen, 1977).

4.5 Conclusion

This study has shown that some men after robot-assisted radical prostatectomy are at increased risk of clinically significant consequences from cardiovascular disease within ten years of their surgery and do suffer with clinically significant levels of fatigue. Clinicians should consider including these factors in the discussion when counselling patients about robot-assisted radical prostatectomy. Additionally, this study has revealed that men after robot-assisted radical prostatectomy appear to meet the recommended guidelines for aerobic physical activity but do not meet them for resistance-based exercise. Future research is needed to establish whether exercise interventions can improve health and fatigue levels in this population.

CHAPTER 5

INTERVENTION DEVELOPMENT

5.0 Intervention Development

5.1 Introduction

Patients who have been treated for prostate cancer are advised to be regularly active and undertake exercise however, there are no published guidelines for this within the United Kingdom despite a recommendation by NICE (National Institute for Health and Care Excellence, 2013). In order to develop an exercise programme that will benefit prostate cancer patients it is important to involve patients in the design of the intervention and in the feedback process (Bagley et al., 2016). Recently, patient and public involvement (PPI) has become an integral part of health care research ensuring that research is relevant, drawing on real-life experiences of patients to inform every aspect of a project, from identification of the question to design, implementation and dissemination allowing researchers to understand what matters to prostate cancer patients (Gamble et al., 2014). PPI allows research to be developed with valuable insight into the best strategies to optimise patient health and experience (McKirdy, 2015).

The role of physical activity in symptom management, reducing risk of reoccurrence and improving quality of life for cancer patients has been a growing topic of investigation in recent years. ACSM recommend that adults having received cancer treatment should complete aerobic exercise on 3-5 days a week, resistance exercise 2-3 days a week and flexibility daily (Riebe et al., 2017). Although resistance exercise training is advised in conjunction with aerobic exercise, it is evident from the previous chapter that aerobic exercise is completed regularly with limited resistance exercise activities are undertaken in prostate cancer patients who have received either robot-assisted radical prostatectomy or ADT. Resistance exercise has recently been demonstrated to be a safe mode of exercise for clinical populations with limited evidence of adverse events (Ashton et al., 2018). By increasing the amount of resistance exercise within this population it is possible to improve cardiometabolic risk factor profile, lower the risk of all-cause mortality and CVD events and improve the patient reported outcomes (Ashton et al., 2018; Garber et al., 2011).

Traditionally, resistance exercise has been used to improve muscular strength, mass and endurance with extensive research being conducted in this area. However, due to an increase in body fat, decrease in lean mass, perceived poor body image and a reduction in $\dot{V}O_2$Peak in the weeks post-surgery it is important that any exercise programme provided to this population also targets these issues (Institute of Medicine National Research Council, 2006; Schmitz, 2010). Previous studies in prostate cancer patients have focused on quality of life, upper and lower body strength, and fatigue as the primary outcomes (Galvao et al., 2006; Norris et al., 2015; Santa Mina, Alibhai, et al., 2013; Segal et al., 2009; Winters-Stone, Dobek, et al., 2015) with few directly investigating cardiometabolic health, although several have reported cardiometabolic variables as secondary outcomes. It is possible for resistance exercise training to be manipulated to improve $\dot{V}O_2$Peak and cardiometabolic health whilst simultaneously achieving improvements in muscle strength. It has been suggested that resistance exercise performed in a circuit, with minimal rest between exercises, can maintain an elevated heart rate and improve $\dot{V}O_2$Peak whilst improving strength, body composition and cardiometabolic health (Ashton et al., 2018; Antonio Paoli et al., 2013; Romero-Arenas et al., 2013; Schmitz, 2010; Wilmore et al., 1978).

Furthermore, previous studies in prostate cancer patients have involved either lifestyle interventions and/or supervised exercise (Bourke et al., 2011; Cormie et al., 2015; Owen et al., 2017; Taaffe et al., 2017; Winters-Stone, Dieckmann, et al., 2015), and whilst these programmes have shown that structured, class-based exercise interventions are effective in improving physical fitness and health outcomes, they are often expensive to implement and sustain over the longer term (K. L. Fisher et al., 2017). Barriers also exist to participation in exercise interventions for older adults including cost, lack of transportation, or disinterest in structured, group-based exercise (K. L. Fisher et al., 2017). However, it has previously been suggested that home-based exercise programmes that promote self-managed exercise have the potential to improve exercise behaviour at a lower cost whilst being more convenient for the patient (G. A. Tew et al., 2015). Therefore, the aim of this chapter is to conduct intervention development sessions with robot-assisted radical

prostatectomy and ADT patients to develop and refine exercises that will be combined to form a home-based resistance training programme that optimises cardiovascular and cardiopulmonary health.

5.2 Methods

This section describes the development of the home-based resistance exercise intervention. Ethics approval was granted by Northumbria University Ethics Committee. Approval was then obtained (ref: 202404) from the Health Research Authority (Appendix 1a). Ethics approval from NHS REC South Scotland was obtained on 8th September 2016 (ref: 16/SS/0143; Appendix 1b) and further approved by NUTH Research and Development on 11th October 2016 (ref: 7832; Appendix 1c). The study was conducted according to the Helsinki Declaration (1964; revised 2001).

5.2.1 Patient and Public Involvement

An initial patient and public involvement session at a local Prostate Cancer Support Group was attended. The session involved providing patients with an overview of the proposed trial and gaining their feedback on initial ideas surrounding research design, recruitment strategies, and suitable outcome measures. Twenty-eight prostate cancer patients at varying stages of different treatments were present along with a Consultant Surgeon and Nurse Specialist.

5.2.2 Design

To inform the development of the exercise intervention, intervention development sessions were conducted, a full description of which is presented in section 5.2.6. The intervention was developed over three sessions separated by a period of 1-2 weeks. All sessions took place in a designated room at The Freeman Hospital. The first two sessions began with discussion regarding current exercise levels, type of exercise currently undertaken and

opinions of exercise. Exercises were then performed with feedback provided during and at the end of the session. The full discussion schedule is available in Appendix 3a. A medical professional was present for both sessions. The third session allowed participants to provide feedback on the developed intervention and exercise manual.

5.2.3 Participants

The patients were identified from NUTH outpatient clinics. A Consultant Urological Surgeon or Prostate Cancer Specialist Nurse initially approached all participants before the researcher. Thirteen prostate cancer patients, treated via either surgery or ADT, were recruited to the study. All participants were informed of the design, requirements and possible risks of the study after which they provided informed consent. All participants were free to withdraw from the study at any time.

5.2.4 Eligibility Criteria

Patients were recruited if they had: (1) histologically-confirmed prostate cancer, (2) treated history of treatment for prostate cancer through robot-assisted radical prostatectomy or ADT, (3) the ability to provide written informed consent and, (4) the ability to communicate to a group to provide feedback on the resistance exercise intervention. Patients were excluded from the study if they were receiving any other treatment for prostate cancer or participating in another clinical trial where concurrent participation was deemed inappropriate.

5.2.5 Physical Activity Levels

Over a 2-week period, participants completed the SPAQ at the end of each week as a recall questionnaire. The SPAQ has good reliability (Cronbach's alpha = 0.998) (Lowther et al., 1999) and is used to assess MVPA over the

previous 7 days. The questionnaire includes sections for both leisure time and occupational physical activity, with each section containing questions on general activity such as walking, stair climbing and manual labour (Lowther et al., 1999). The mean total MVPA was calculated in addition to the mean total for each individual component.

5.2.6 Intervention Development Session

In sessions 1 and 2 the participants were then taken through a series of resistance exercises using Thera-bands (Table 10) with the researcher ensuring correct technique and providing teaching points for each exercise. The exercises were a combination of single- and multi-joint exercises to proke a strong cardiovascular stimulus whilst being acceptable for patients to perform. Participants were provided with heart rate monitors (Polar O.Y., Finland) to wear for the duration of the exercises. Ratings of perceived exertion (RPE) were measured using the OMNI-RES scale to assess the effort of participants during the exercises. After completing the exercises, the participants had the opportunity to provide feedback on the exercises, how they could be transferred into the home environment, the intervention as a whole and how they would feel about being prescribed such an intervention as part of their treatment. Once the intervention had been developed, a group of patients were invited back to the Freeman Hospital for session 3 to provide feedback on the developed exercise manual and the resistance training intervention. All intervention development sessions were audio-recorded using a Dictaphone.

Table 10. Exercises completed during sessions 1 and 2.

Session 1	Session 2
Wide stance squat	Wide stance squat
Lunge	Singles leg press
Reverse abdominal curl	Abdominal curl
Chest press	Chest press
Bicep curl	Bicep curl
Reverse flies	Bent over row
Upright row	Lateral raise
Elbow kick back	Elbow extension

5.2.6 Analysis

Verbatim transcription was conducted by a medical secretary and checked by the researcher. The general inductive thematic analysis approach was used to identify themes in the text data relating to the study objectives (Cooper, 2012; Thomas, 2006). Once familiarised with the data, initial codes were generated in which themes arose from. The following themes were derived from the transcripts: (1) current exercise and perceptions of resistance exercise, (2) motivation for exercise and, (3) resistance exercise programme structure.

5.3 Results and Discussion

5.3.1 Participants

A total of 13 participants (6 robot-assisted radical prostatectomy and 7 ADT) with a mean age of 63.4 ± 8.8 years (body mass 84.6 ± 12.5 kg) took part in the development sessions. All participants had all received treatment for prostate cancer within the previous 18 months.

5.3.2 Patient and Public Involvement

Patient and public involvement within health research has steadily grown worldwide over the last few decades (Pii, Schou, Piil, & Jarden, 2019). As a result, INVOLVE was established in 1996 with the aim of advancing patient involvement in research. Patient and public involvement helps to make research projects more relevant, improve the patient research experience and to help define what is acceptable to potential participants (INVOLVE, 2016). In cancer research, patient and public involvement ensures that research to improve medicines, technologies, treatment and care corresponds with the needs and priorities of those affected by cancer.

Initial patient and public involvement sessions were conducted with a group of prostate cancer pateints prior to the ethics application for this project. These early sessions allowed patients to provide input on the design of the project for example, length of intervention, frequency of testing sessions and type questionnaires used. Additionally the sessions highlighted patient concerns surrounding safety of maximal exercise testing after surgery and the relevance of maximal exercise in their daily lives. Unlike maximal testing, submaximal testing does not require medical supervision however does result in less accurate assessment of cardiopulmonary exercise capacity. As a result of the patient feedback, the protocol was changed to encorporate submaximal testing of strength and aerobic capacity. Furthermore, a patient representative was appointed who was consulted on all aspects of the project and any amendments made to the relevant ethics committees.

5.3.3 Current Exercise and Perceptions of Resistance Exercise

All participants reported being active on a weekly basis and this is evident from the SPAQ data (Table 11).

Table 11. Reported physical activity levels over a 2-week period using the SPAQ.

	Average Minutes
Total MVPA	651.7 ± 205.5
Walking	309 ± 182.6
Manual labour	113.2 ± 145.8
Active housework	56.4 ± 80.1
Dancing	0 ± 0
Sport/Leisure activities	149.9 ± 219.8
Other activities	23.2 ± 59.4
All data presented as mean ± SD. MVPA – moderate to vigorous physical activity	

The most common sport/leisure activities reported included walking football, cycling and tennis. All participants reported that post-treatment they tried to increase the amount of walking they were completing on a daily basis however one participant commented on how tiring increasing walking mileage had been for him:

"I was in agony… I don't think I have to come to terms that I can't do as much as I used to" (Participant 3, age 74 years)

Another participant talked briefly about the barriers to exercise and stated that:

"I hibernate during the winter" (Participant 1, age 60 years)

Weather is a commonly reported barrier to exercise with it being reported in both colorectal and breast cancer patients (Courneya et al., 2005; L. Q. Rogers, Courneya, Shah, Dunnington, & Hopkins-Price, 2007; Laura Q. Rogers et al., 2006). In a previous study primarily examining the barriers to exercise, approximately 35% of prostate cancer patients reported bad weather

as a barrier to exercise behind being ‘too busy’ and ‘having no willpower’, therefore this finding is not surprising (Ottenbacher et al., 2011). These barriers may help in the development of future trials with potentially more home-based exercise interventions used to try to alleviate the effects of bad weather and being too busy as barriers to exercise participation.

The participants were questioned by the researcher on their perceptions of resistance exercise and provided the following responses:

“I tend to avoid weight training as I don’t really want to build muscle, but I believe now that it is potentially beneficial” (Participant 2, age 67 years)

“I thought cardiovascular exercise I thought was more beneficial… didn’t realise resistance exercise could help burn fat” (Participant 2, age 67 years)

“The exercise man at Maggie’s, because I tend to go to that on a Tuesday, told me that if you do more reps and a lighter weight it will help burn fat but less reps and a harder weight will build muscle, I don’t know if that is right?” (Participant 4, age 57 years)

Such responses suggest a lack of understanding surrounding resistance exercise and its potential benefits. This could be due to a lack of information on this mode of exercise provided by health care professionals at the point of diagnosis and treatment (Smaradottir, Smith, Borgert, & Oettel, 2017). It is unknown how much exercise guidance is currently provided to patients by clinicians however a UK-based study by Daley and colleagues reported that approximately 56% of oncologists and surgeons did not routinely discuss exercise with their patients (Daley, Bowden, Rea, Billingham, & Carmicheal, 2008). Additionally it has been stated that 58% of nurses are unaware of research surrounding exercise training for cancer rehabilitation and 33% reported receiving no training relating to exercise and health for cancer patients (Stevinson & Fox, 2005). Furthermore, only 31% of colorectal cancer patients could recall being provided with exercise advice during consultations (A. Fisher, Williams, Beeken, & Wardle, 2015). Despite this, exercise has been shown to be safe for cancer patients to perform over the course of the cancer

continuum and could improve the outcomes for some cancer survivors (A. Fisher et al., 2015; Institute of Medicine National Research Council, 2006).

5.3.4 Motivation for Exercise

All participants discussed the difficulties of exercising in the home and the self-motivation required with one participant stating:

"I used to run a lot… the hardest thing to do was to put my shoes on. Once you've got your shoes and your kit on, you're out there then, doing it is not a problem, it's just switching your mind on to do it basically. Making the time and do it when you decide to do it." (Participant 1, age 60 years)

Research into exercise adherence and motivation has previously been mixed in cancer populations. Some studies suggest that the strongest correlates of exercise adherence among women treated for breast cancer are not demographic, socioeconomic, or medical variables but rather social and cognitive variables such as attitudes, perceived behavioural control and subjective norms (Jones & Courneya, 2002; Ottenbacher et al., 2011). Courneya et al. (Courneya et al., 2008) argue that such social and cognitive variables are not predictors of exercise adherence and suggest that patients who enrol in exercise interventions are already motivated to engage in exercise, an observation reflected by the fact that although adherence to exercise trials is high, uptake into these trials is generally low (Courneya et al., 2008; Maddocks, Mockett, & Wilcock, 2009). Knowledge of these barriers to exercise participation has been suggested to aid the optimal design of targeted physical activity interventions among prostate cancer survivors and should result in long-term exercise adherence within the population (Gho, Munro, Jones, & Steele, 2014; Ottenbacher et al., 2011).

The researcher asked participants how the study could be designed in order to improve patient motivation and improve adherence to the exercise intervention. One participant responded with:

"Tick box, so when I've done the exercises, I know I've done them. So, if I haven't done the exercises, I feel guilty" (Participant 7, age 60 years)

Another participant suggested having some information surrounding goal setting within the exercise manual as it:

"Keeps you focused, gives you a target" (Participant 6, age 57 years)

After some discussion between the researcher and participants, it was concluded that a goal setting page should be included in the final exercise manual along with an exercise diary to allow patients to monitor their progression. It has been reported that tasks such as goal setting and self-monitoring alongside some support increases adherence to exercise interventions and promotes long-term physical activity (Chao, Foy, & Farmer). Support would be given to patients in the exercise group in the form of a weekly telephone call. This would allow the researcher to monitor their progression and provide encouragement through the intervention alongside providing patients the opportunity to discuss any problems and barriers to maintaining the adherence to the intervention (Chao et al.; Room, Hannink, Dawes, & Barker, 2017).

5.3.5 Resistance Exercise Programme Structure

Exercise selection for the sessions was based on some of the resistance exercise interventions used in previous studies (Table 12). The ability for the exercises to be performed using Therabands within the home environment with minimal equipment also influenced the exercises selected.

Discussion regarding the structure of the exercise intervention took place in both sessions 1 and 2. Whilst performing the exercises participants wore heart rate monitors which were checked by the researcher at multiple intervals. The exercises elicited heart rates between 100 bpm and 130 bpm, equating to 40-70% heart rate reserve, for all participants but varied between the age of the participants and the different exercises. ACSM (Riebe et al., 2017) recommends beginning exercise interventions at heart rates between 40-60%

heart rate reserve for overweight individuals to assist with fat loss. Participants commented on what exercises they found difficult to perform:

"The one where you did the lunge forward (Figure 8) I really struggle with that… I really struggle with balancing for that. The one where you sit down and push the leg out, I found it much easier." (Participant 2, age 67 years)

Another participant who reported existing back pain and mobility issues commented that:

"The lower abdominal crunch (Figure 9) was hard for me… Truck curl (Figure 10) up was easier" (Participant 10, age 71 years)

Table 12. A selection of studies employing resistance exercise interventions in prostate cancer patients.

Paper	Resistance Exercise Intervention	Exercises
Cormie et al. (2015)	12 weeks 2 days/week 1-4 sets, 6–12 Repetition Maximum (RM) 60–85% of 1RM	Leg press, leg extension, leg curl, calf raise, chest press, latissimus pull-down, biceps curl and triceps extension
Courneya et al. (2004)	12 weeks 3 days/week 2 sets, 8-12 reps 60-70% 1RM	Leg extension, leg curl, calf raises, chest press, latissimus pull-down, overhead press, triceps extension, biceps curls, and modified curl-ups
Galvao et al. (2006)	20 weeks 2 days/week 2-4 sets, 6-12 RM	Chest press, seated row, shoulder press, latissimus pull-down, triceps extension, biceps curl, leg press, squat, leg extension, leg curl, abdominal crunch and back extension
Galvao et al. (2009)	24 weeks 2 days/week 2-4 sets, 6-12 RM	Chest press, seated row, shoulder press, leg press, leg extension, leg curl and abdominal crunches
Norris et al. (2015)	12 weeks 3 days/week 2 sets, 8-12 reps 60-80% 1RM	Chest press, leg press, latissimus pull-down, leg curl, shoulder press and leg extension
Santa Mina, Alibhai, et al. (2013)	24 weeks 3-5 days/week 2-3 sets, 8-12 reps 60-80% 1RM	Ball squats, hamstring curls, push-ups, upright rows, triceps extensions, bicep curls, seated row, lateral raises, ball abdominal crunches and hip extensions
Segal et al. (2003)	12 weeks 3 days/week 2 sets, 8-12 reps 60–70% of 1RM	Leg extension, calf raises, leg curl, chest press, latissimus pull-down, overhead press, triceps extension, biceps curls, and modified curl-ups
Segal et al. (2009)	24 weeks 3 days/week 2 sets, 8-12 reps 60–70% of 1RM	Leg extension, leg curl, seated chest fly, latissimus pull-down, overhead press, triceps extension, biceps curls, calf raises, low back extension, and modified curl-ups

Figure 8. Lunge performed with a Theraband.

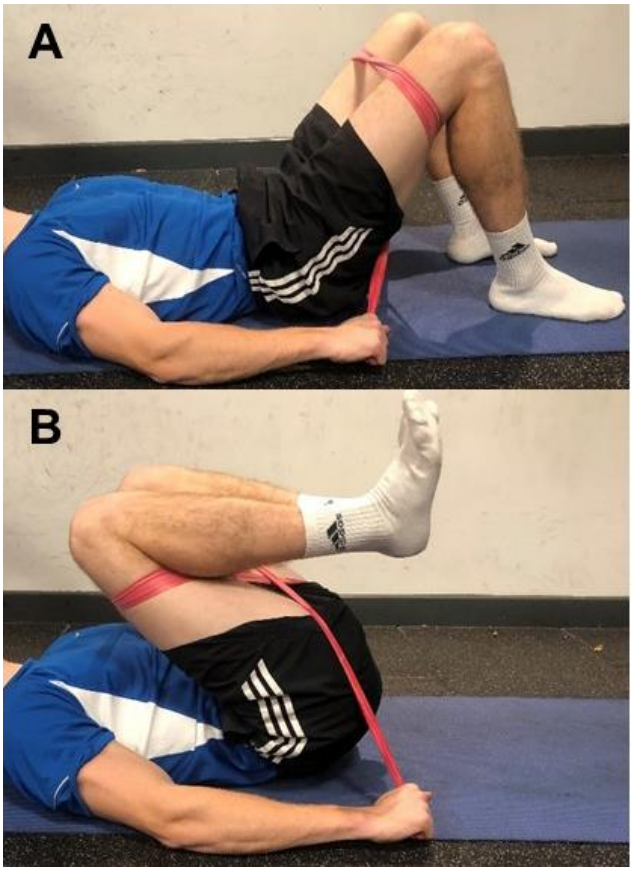

Figure 9. Lower abdominal crunch performed with a Theraband (A) starting position, (B) end position.

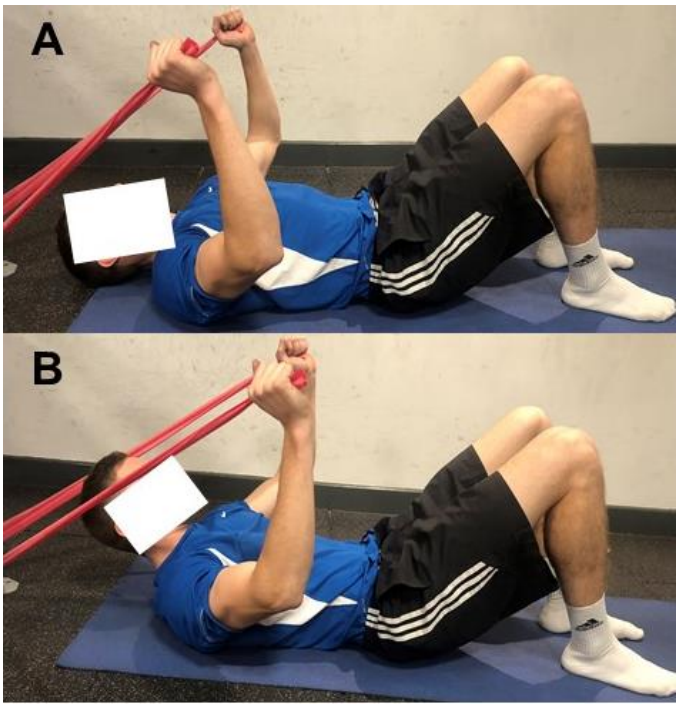

Figure 10. Truck curl up performed with a Theraband (A) starting position, (B) end position.

As a result of this feedback it was decided by the research team that both balance and back pain could be common issues in the age group to be studies in the main trial. Due to this, the lunge was excluded, and a standing abdominal exercise was included.

The structure was based on ACSM guidelines for cancer survivors alongside the design of the studies mentioned in Table 12. The ACSM recommends that cancer survivors after surgery should be allowed adequate time to heal before undertaking moderate to vigorous aerobic exercise 3-5 days a week and moderate intensity (60-70% 1RM) resistance exercise 2-3 days a week (Riebe et al., 2017). ACSM states that resistance exercise should consist of at least 1 set of 8-12 repetitions and target all major muscle groups (Riebe et al., 2017). In addition, upon discussion of the intervention, participants had varying opinions as to the structure. Some participants commented that they would

prefer to be given a set programme to follow where as others stated that they would like to have some choice as to what exercises they wished to do.

"Rather than doing the same thing day to day it is sometimes nice to change it about a bit… some core ones and to mix and match others in" (Participant 5, age 48 years)

Due to such a variety of feedback, the research team suggested that every patient would receive an individualised exercise programme. They would also be provided with a bank of exercises to allow them to swap exercises within the same muscle group should they wish to have some flexibility within the intervention.

As a result of the feedback from sessions 1 and 2, a manual was developed and in session 3, a group of patients were asked to provide feedback on the exercise manual. The final manual can be found in Appendix 3b. Below is a selection of the comments received:

"Might be useful to have a little schematic showing you should feel tension in this muscle" (Participant 2, age 67 years)

"Remind people to breathe… people do hold their breath" (Participant 8, age 62 years)

"Something that I don't think you address in here is the different strengths of the bands" (Participant 13, age 71 years)

A page within the manual had been dedicated to allowing patients to monitor their exercise intensity. The OMNI-RES (Colado et al., 2012) scale has been validated in older adults within the same range as the patients that would be recruited to the trial. When discussing the session intensity and OMNI-RES scale one participant said:

"I found it easier as that told me you know, can you talk to someone, can you… I think a little bit more of a description, just what you mean, I would find useful" (Participant 13, age 71 years)

As a result of such feedback, comments were added onto the OMNI-RES scale to provide more description to the patients at each stage (appendix 3c). At the end of the session participants commented on the manual as a whole:

“I think this is super” (Participant 13, age 71 years)

“It is really good” (Participant 12, age 62 years)

5.4 Conclusion

The research team took on board all the feedback provided by the participants over the three sessions and have included general information on the benefits of resistance exercise, information on the different resistance bands and exercises within the particular muscle group categories. Furthermore, behaviour change techniques were included in the manual including goal setting and self monitoring via an exercise diary, as a result of patient feedback. The exercise intervention would be individualised to each patient from a bank of exercises at the back of the manual. The intervention involves patients completing 3 sessions a week of the resistance exercise programme completing 3 sets of 10-15 reps in accordance with and progressed accordingly following ACSM guidelines (Riebe et al., 2017). All exercises are to be completed back-to-back with little rest between in order to maintain an elevated heart rate and oxygen consumption to aid adaptations to the cardiovascular system alongside muscular adaptions (Romero-Arenas et al., 2013; Schmitz, 2010; Wilmore et al., 1978).

CHAPTER 6

CLINICAL TRIAL

6.0 Clinical Trial

6.1 Introduction

Robot-assisted radical prostatectomy is an established minimally-invasive treatment for localised or locally-advanced prostate cancer, but often has an impact on both physical and mental well-being (J. J. Aning et al., 2018; Ansmann et al., 2018). Often patients experience side effects of treatment such as erectile dysfunction and urinary incontinence along with reduced quality of life (Bang & Almallah, 2016; Jeldres et al., 2015). It has also been documented in Chapter 4 of this thesis that patients who have received robot-assisted radical prostatectomy are at an increased risk of a heart attack or stroke within the next 10 years compared to the average male of the same age. Additionally, it is possible that due to limited physical activity after surgery, unfavourable changes in body composition occur further impacting upon the risk of cardiovascular disease.

There is a lack of research investigating exercise prescription within the robot-assisted radical prostatectomy patient group and therefore no exercise recommendations currently exist within this pathway of care. NICE however, does recommend structured exercise programmes tailored to individuals receiving ADT for prostate cancer and for other health conditions such as myocardial infarction, stroke, chronic heart failure, chronic obstructive pulmonary disease, depression, lower back pain and chronic fatigue syndrome (National Institute for Health and Care Excellence, 2014a, 2014b). Exercise after diagnosis may help to reduce overall prostate cancer mortality and improve quality of life, therefore, exercise advice as part of the treatment pathway could be vital (Bourke et al., 2014; Kenfield et al., 2011). A recent systematic review demonstrated that exercise is generally safe and well tolerated in prostate cancer patients and should be considered an important component of prostate cancer care due its positive effects on fitness and physical function, and reduction of fatigue (Moe et al., 2017).

RET over a 6-month period has recently been shown to improve systolic and diastolic blood pressure, arterial function, $\dot{V}O_2$Peak, blood lipid profile and, fasted insulin and glucose levels in both healthy and those with an adverse

cardiometabolic risk profile (Ashton et al., 2018). Additionally, a recent study investigated 3 months of RET, in combination with walking, and demonstrated improved urinary incontinence, however, this study was conducted in elderly women (Talley, Wyman, Bronas, Olson-Kellogg, & McCarthy, 2017). The evidence base for RET in those treated via robot-assisted radical prostatectomy is currently limited, however it is possible to hypothesise improvements in cardiometabolic health and urinary incontinence may occur.

The majority of studies examining the effects of RET comprise of supervised exercise programmes (Almenning et al., 2015; Greenwood et al., 2015; Kemmler, Wittke, Bebenek, Frohlich, & von Stengel, 2016; O'Connor et al., 2017; Segal et al., 2009). However, these programmes involve participants travelling to the centre which can be costly and time consuming, and so home-based programmes have been suggested as a method of combating this. Home-based exercise is convenient for participants, relatively low cost to implement and provide an alternative and flexible way to exercise for older adults who are unable to carry out traditional RET or have access to gym facilities (Chuter, de Jonge, Thompson, & Callister, 2015; Thiebaud, 2014). Despite the benefits of home-based exercise to the participants, there are concerns with this type of exercise with regards to adherence and sufficient exercise progression (Thiebaud, 2014).

The aim of this study was to assess the effects of a home-based progressive resistance exercise programme following robot-assisted radical prostatectomy in prostate cancer patients to counteract the adverse side effects of treatment.

6.2 Methods

The development of this trial followed the Medical Research Council's (MRC) published guidelines on ethical issues along with guidance on consent, policy on risk management, developing clinical trials and clinical trial regulations (Medical Research Council, 2018). The Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed to guide the reporting of this study (Schulz, Altman, & Moher, 2010).

6.2.1 Ethical Approval

University ethical approval was granted by Northumbria University Ethics Committee. Approval was then obtained (ref: 202404) from the Health Research Authority (Appendix 1a). NHS ethical approval from NHS REC South Scotland was obtained on 8th September 2016 (ref: 16/SS/0143; Appendix 1b) and further approved by NUTH Research and Development on 11th October 2016 (ref: 7832; Appendix 1c). The trial was prospectively registered on the International Standard Randomised Controlled Trial Number (ISRCTN) database (ref: ISRCTN10490647).

6.2.2 Research Governance and Good Clinical Practice

This research recruited participants with prostate cancer from one NHS site. To ensure participant safety and confidentiality, the researcher received Good Clinical Practice training with all research being conducted in accordance within these guidelines. The study was conducted according to the Helsinki Declaration (1964; revised 2001).

6.2.3 Study Design

This study was a single-site, two-arm randomised controlled trial. Randomisation was conducted after the screening and baseline assessment on a 1:1 basis by an external investigator not directly involved with the trial. Initial follow-up was conducted at 12 weeks and a further follow-up session at 24 weeks. A schematic of the trial design is presented in Figure 11.

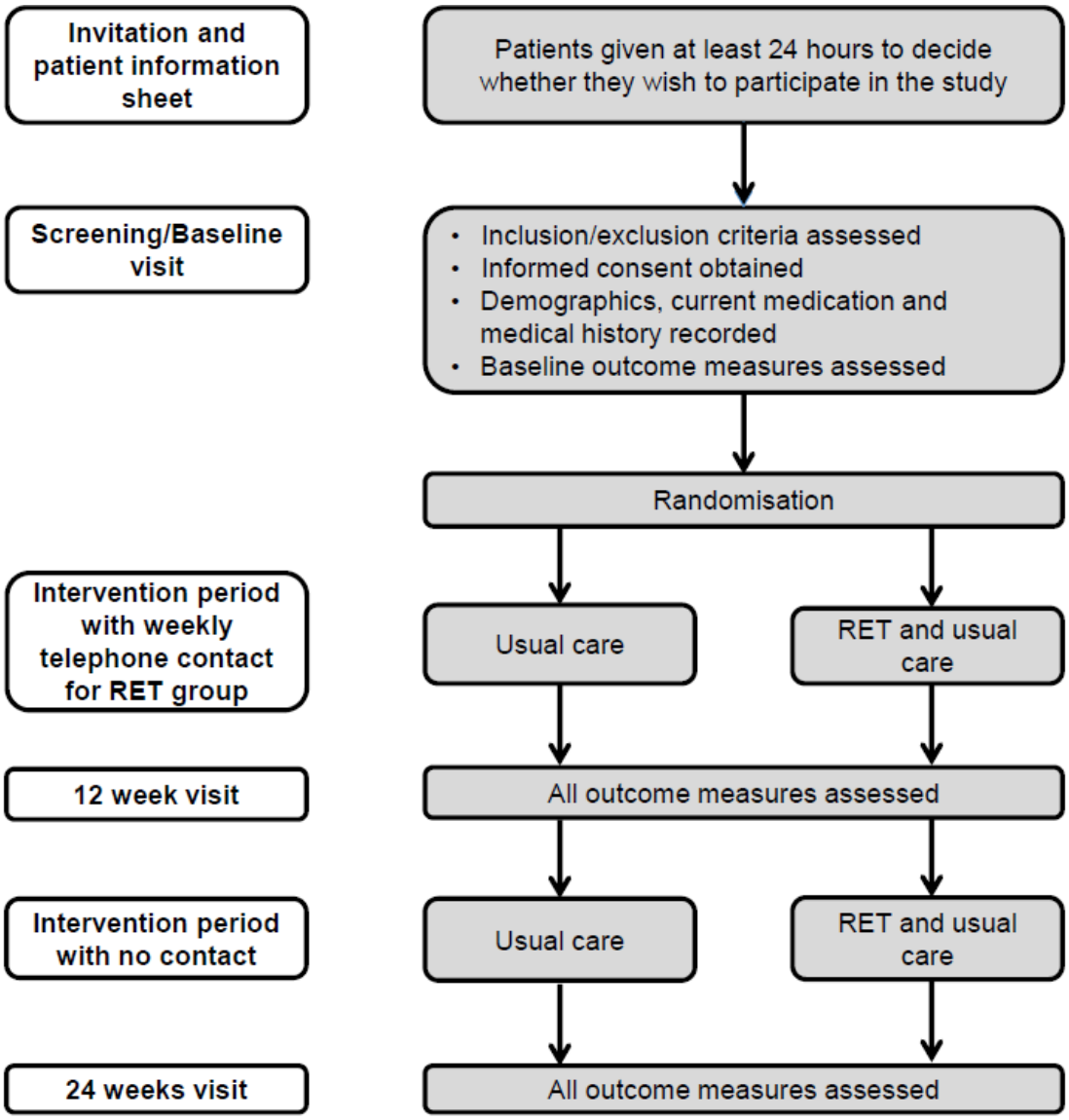

Figure 11. Schematic of the trial design.

6.2.4 Recruitment

The patients were identified from NUTH outpatient clinics. A Consultant Urological Surgeon or Prostate Cancer Specialist Nurse initially approached potentially eligible patients before the researcher provided the patient with an information sheet. All patients were recruited to the study 8-12 weeks after surgery. All patients who responded to the patient information sheets were fully

informed of the study protocol and requirements and, considered for eligibility through an initial screening visit to ensure that they met all inclusion criteria. Upon successfully meeting these criteria, participants signed an informed consent form as per the MRC guidelines (Medical Research Council, 2018) before being entered into the study and data collection schedule planned. All participants were free to withdraw from the study at any time.

6.2.5 Participants

Inclusion Criteria

- Men having undergone the robot-assisted radical prostatectomy procedure in the last 8-12 weeks after being diagnosed with prostate cancer
- Completed a cardio-pulmonary exercise test (CPET) within the previous 4 months
- Able to provide consent
- Able to read and speak English to a level allowing satisfactory completion of written consent and questionnaires

Exclusion Criteria

- Participation in another clinical trial where concurrent participation is deemed inappropriate by a clinical investigator
- Receiving any other treatment for cancer
- Planned further surgery within the first 3 months after being randomly assigned to a group
- Unsuitable for resistance exercise training based on opinion of the clinical investigator

All data were collected at The Freeman Hospital, Newcastle upon Tyne. Prior to any testing all participants underwent checks of resting heart rate and blood pressure, and a 12-lead echocardiogram (ECG) configuration was used to assess real-time cardiac function. The ECG was conducted at rest and was interpreted and checked for any abnormalities by a medical professional.

Participants with no contraindications to exercise were allowed to continue into the study.

6.2.6 Intervention

The intervention group were asked to complete three resistance exercise sessions each week for 24 weeks (Borde, Hortobagyi, & Granacher, 2015; Lachman, Neupert, Bertrand, & Jette, 2006). Participants completed 3 sets of 12-15 reps on each exercise in a circuit manner (Chodzko-Zajko, 2009; Ratamess, 2009). All participants began performing 7 exercises targeting each major muscle group such as legs (squat, leg press, quick kicks), abdominals (trunk curl-up, lower abdominal crunch, side bend), back (bent-over row, reverse flies), chest (chest press), shoulders (upright row, lateral raise, front raise), and arms (bicep curl and either elbow extension or elbow kick back). Participants had the choice to add in additional exercises from those provided and were asked to document any changes and their adherence in an exercise diary. The exercises were performed in a circuit with 30-60 seconds rest at the end of each circuit until 3 full circuits had been performed. The exercise programme was progressed according to the ACSM guidelines and the OMNI-RES Scale (Riebe et al., 2017). Participants were either instructed to alter the hand/foot position on the band to increase resistance or, to progress onto the next level of resistance band once 7-8 was reached on the OMNI-scale (Colado et al., 2012).

Participants in the intervention group were invited to take part in 3 supervised exercise sessions in the first week. In week 2, participants were invited to 2 supervised sessions and 1 in the home environment (i.e., unsupervised). During weeks 3 and 4, participants were invited to 1 supervised session and 2 completed at home. All supervised sessions took place in a designated room at The Freeman Hospital. During weeks 5 to 12, all exercise sessions were unsupervised, but participants in the intervention group received weekly telephone contact from a member of the research team (Hackshaw-McGeagh et al., 2017). Those who did not take up the invite of supervised sessions were contacted weekly via telephone from week 1. During weeks 12 -24, all sessions

were unsupervised with no contact from the research team. An exercise diary was used to record their RET activity levels over the 24 weeks.

The control group were instructed to continue with their usual activity levels; their usual care was not affected by this trial.

6.2.7 Outcome Measures

All outcome measures were assessed in all participants at baseline (0 weeks), mid-way (12 weeks) and on completion of the trial (24 weeks). All follow-up sessions were conducted within the week surrounding the final exercise session to allow for participants' availability.

6.2.7.1 FMD

For FMD assessments, a manual sphygmomanometer was placed distal to the olecranon process, with arterial imaging of the brachial artery performed using an ultrasound machine (Zonare, z.one ultra, United States of America) on the upper arm. Resting measurement of vessel diameter was performed for 1 min before cuff inflation to a pressure 50 mmHg above SBP. Occlusion was maintained for 5 min. Recordings were restarted 30 secs before cuff release and continued for a further 3 min thereafter (Thijssen, 2011). FMD measurements were completed at each assessment visit. Measurements of the artery diameter were taken along with the shear rate. Analysis of FMD recordings was completed using Cardiovascular Suite software (Quipu v3.4, 2018). Measurements of baseline diameter (mm), maximum diameter (mm), recovery diameter (mm), baseline shear rate (s^{-1}), maximum shear rate (s^{-1}), area, area to maximum, FMD (%) and FMD with respect to recovery diameter (FMDr %) were all recorded.

6.2.7.2 Blood Sampling

A total of 13 ml of whole blood was collected using 3 vacutainers at baseline, 3 months and 6 months. An SST tube containing spray-coated silica and a polymer gel was used for blood lipid analysis (5 ml). An EDTA tube was used for insulin analysis (6 ml) and a fluoride tube for glucose analysis (2 ml). Insulin resistance was calculated using the formula below (Matthews et al., 1985):

$$\text{HOMA-IR} = \frac{\text{Fasting insulin x Fasting glucose}}{405}$$

All blood samples collected were analysed by the Pathology Department of The Freeman Hospital, Newcastle upon Tyne.

6.2.7.3 Anthropometric Profile

Body mass (Seca Ltd, Seca Scales 709, Birmingham, UK) and stature (Seca Ltd, Seca 220 Stadiometer, Birmingham, UK) were recorded at all assessment visits. All skinfold assessments were completed in accordance with ISAK guidelines (Marfell-Jones, 2012) with the researcher ISAK Level 1 qualified. Skinfold assessments took place in a private room maintained as close to 20°C as possible for the participants comfort. Participants were asked to wear shorts and if comfortable to remove clothing from the waist upwards. Participants were asked to stand in the anatomical position and breathe normally throughout. Skinfolds using callipers (British Indicators, Harpenden, Sussex, UK) were taken at seven sites: triceps, subscapular, biceps, iliac crest, supraspinale, abdominal, front thigh and medial calf. Four girths were also taken using a body composition tape measure (tape): arm relaxed, arm flexed and tensed, waist (minimum) and gluteal. Finally, two breadths were measured using small sliding callipers: biepicondylar humerus and biepicondylar femur. Each skinfold, girth and breadth measurement was taken at least twice at each assessment visit with body fat percentage, and the sum of 6 and 8 skinfolds being calculated (Australian Sports Commission, 2004).

6.2.7.4 Submaximal Aerobic Capacity

Participants performed a submaximal incremental walking protocol in the form of the Bruce ramp protocol on a motorised treadmill (Life Fitness, Next Gen 9500 Treadmill, Cambridge, UK). The protocol comprised of 1-minute intervals in which both the speed and gradient increased (Riebe et al., 2017). The exercise test was terminated when the participant reached 15 on Borg's 6-20 Rating of Perceived Exertion (RPE) Scale (Kaminsky & Whaley, 1998) or for safety if the participant demonstrated an abnormal response to exercise such as a very high heart rate, chest pain, light headedness and dyspnea. Clinical cover and an on-call physician were available during all testing procedures in the event of an adverse reaction to exercise. $\dot{V}O_2$Peak was estimated from the level reached by the participant and using the ACSM Guidelines for Exercise Testing and Prescription (Riebe et al., 2017).

6.2.7.5 Strength

Exercises from the senior fitness test were used to evaluate upper and lower body strength in the participants. The elements used from the senior fitness test is available in Appendix 4a. Lower body strength was assessed through the chair stand test. This required participants to sit on a chair with their feet flat on the floor and knees at a right angle. Participants were then required to repeatedly stand up from and sit down on a chair for 30 seconds. Upper body strength was assessed through the bicep curl test and requires men to repeatedly lift an 8 lb (3.63 kg) weight for 30 seconds. Both strength tests were completed at each assessment visit.

6.2.7.6 Cardiovascular Health

The risk of suffering a heart attack or stroke within the next 10 years was calculated using Q-Risk2 (Hippisley-Cox et al., 2008). Q-Risk2 score is calculated from patient-reported family history, age, gender, ethnicity, socio-economic status, and physiological measurements (e.g. SBP, medication, total

cholesterol and HDL cholesterol ratio), and can be categorised as < 10% (low), 10%-20% (medium) or > 20% (high) (Coghill et al., 2018).

6.2.7.7 Questionnaires

Questionnaire booklets (Appendix 4b) were administered to the participants at each assessment visit at baseline, 12 and 24 weeks after entering into the trial. Participants were provided with full instructions on how to complete the questionnaire booklet. The questionnaires used were the EQ-5D-5L quality of life, FACT-P prostate cancer specific quality of life, the Godin Leisure Time Exercise questionnaire (modified) and the BFI. All permissions were sought prior to questionnaire use.

The EQ-5D-5L was used to assess health-related quality of life in participants and has previously been validated in both cancer and diabetic populations (Janssen, Lubetkin, Sekhobo, & Pickard, 2011; Pickard, Wilke, Lin, & Lloyd, 2007). The questionnaire comprises of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The five responses represent a ‘health state’, which is converted using a standard algorithm to produce a single health state index score (Reenen & Janssen, 2015). The additional EQ-VAS was used to record the participants’ self-rated health on a vertical visual analogue scale, providing quantitative data reflecting the participants’ own judgement.

The FACT-P is part of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System and has 39 items grouped into five subscales: Physical Well-Being (PWB), Social/Family Well-Being (SWB), Emotional Well-Being (EWB), Functional Well-Being (FWB) and the Prostate Cancer Subscale (PCS). The PWB, FWB and PCS subscales are combined to yield the FACT-P Trial Outcome Index (TOI). The sum of PWB, SWB, EWB and FWB subscale scores gives the overall FACT-G score with a range from 0 to 108. The PCS score is combined with the overall FACT-G score to form the overall FACT-P score with a range from 0 to 156.

The Godin Leisure Time Exercise Questionnaire (modified) is a short questionnaire that is often used to assess exercise levels in oncology research (Amireault, Godin, Lacombe, & Sabiston, 2015). It is a 4-item self-administered questionnaire with the first three questions seeking information on the number of times one engages in light, moderate or vigorous aerobic activity and the fourth item seeks information on the frequency and duration of resistance exercise.

The BFI is a standard, reliable instrument used to rapidly assess fatigue in individuals with cancer and is significantly correlated with other validated fatigue questionnaires (Mendoza et al., 1999; Sternberg et al., 2013). The purpose of the BFI is to rapidly assess the severity of fatigue and the impact of fatigue on daily functioning over the previous 24 hours in cancer patients. It consists of three questions assessing fatigue severity and six questions assessing the interference of fatigue with the participants mood and social/physical functioning. Fatigue intensity was defined as the score of the current, average and worst levels of fatigue (weariness, tiredness) over the previous 24 hours on a 0–10 scale with 0 = 'no fatigue' and 10 = 'as bad as you can imagine'. Fatigue interference was the average score of all items assessing interference of fatigue with several functional domains such as general activity, mood, walking ability, work, relationships, and enjoyment of life. Each of these six items measures fatigue interference on a 0–10 scale, with 0 = 'does not interfere' and 10 = 'completely interferes'.

6.2.8 Sample Size Estimation

The trial was powered to detect a 2.2% absolute difference between groups in FMD at 12 weeks. Previous studies have indicated that this is a clinically-meaningful difference (Atkinson & Batterham, 2013; Yeboah et al., 2009), and one that was realistic to expect in a parallel-group study in which one group receive a 3-month structured exercise programme (Gilbert et al., 2016). Assuming a standard deviation of 2.8% (Gilbert et al., 2013), the anticipated effect size was approximately 0.80. To observe a difference of this magnitude with 80% power and 5% two-sided significance, a total sample size of 52

participants was required. Allowing for 15% attrition (Bourke et al., 2014), 60 participants were needed in total with 30 participants randomised to each group.

6.2.9 Randomisation

Participants were randomised (1:1) in blocks of 4 to either the RET intervention or control group. Randomisation was conducted by an independent individual not directly involved with the trial using an online random number generator (http://www.randomization.com) after completion of the baseline assessments.

6.2.10 Blinding

Assessments at weeks 12 and 24 that could be influenced by the researcher (e.g. aerobic capacity) were conducted by a trained research assistant who was blind to group allocation.

6.2.11 Statistical Analysis

Multiple imputation was used for any missing data prior to intention-to-treat analysis being conducted (Manly & Wells, 2015). Multiple imputation replicates the incomplete dataset multiple times and replaces any missing data in each replicate with plausible values drawn from an imputation model taking into account the uncertainty associated with the imputed values (Hayati Rezvan, Lee, & Simpson, 2015; Manly & Wells, 2015). Analyses run on the dataset were pooled according to Rubin's (1987) rules (Rubin, 2009). Normality of distribution for outcome measures was tested using the Shapiro Wilks test and assumptions were tested prior to analysis. The effect of the intervention was evaluated using an analysis of covariance (ANCOVA) model. The 12- and 24-week outcomes were the dependent variables and trial arm (RET intervention and usual care) were the independent variables. The baseline value of the outcome was included as a covariate (Vickers & Altman, 2001). The treatment

effect (intervention minus control) is presented with its 95% confidence interval (CI). All analyses were conducted using IBM SPSS Statistics Version 22 (IBM United Kingdom Limited, Hampshire, UK).

6.3 Results

6.3.1 Participants

In total, 73 participants post-robot assisted radical prostatectomy were deemed eligible and were provided with information regarding the study. A flowchart of participant recruitment, randomisation, and completion is presented in Figure 12. Forty-two men post- robot assisted radical prostatectomy were recruited over a 10-month period to take part in the trial. Recruitment ended due to the funding period coming to an end. Participant demographic information is presented in Table 13. Reasons for not taking part in the trial were given by most patients with the hospital being too far to travel the most common (n = 16). Nine patients approached said that they were already very active and so did not think they would benefit from taking part in the trial with a further 2 patients stating they did not have enough time. Four patients could not be contacted after the participant information sheet had been provided.

Participants often had multiple comorbidities in addition to prostate cancer (range 0 - 4) which included hypertension (52.4%, n = 22), hypercholesterolemia (35.7%, n = 15), type 2 diabetes mellitus (11.9%, n = 5), asthma (9.5% n = 4), atrial fibrillation (4.8%, n = 2), arthritis (4.8%, n = 2), and depression (4.8%, n = 2). Two participants dropped out prior to the 12 week follow up (RET n = 1, usual care n = 1) one due to an unrelated back injury and one due to a family bereavement. A further 3 dropped out of the study prior to the 24-week follow up session (RET n = 1, usual care n = 2); one reporting multiple hernias (usual care group) and the remaining 2 not attending the follow-up session and being uncontactable thereafter.

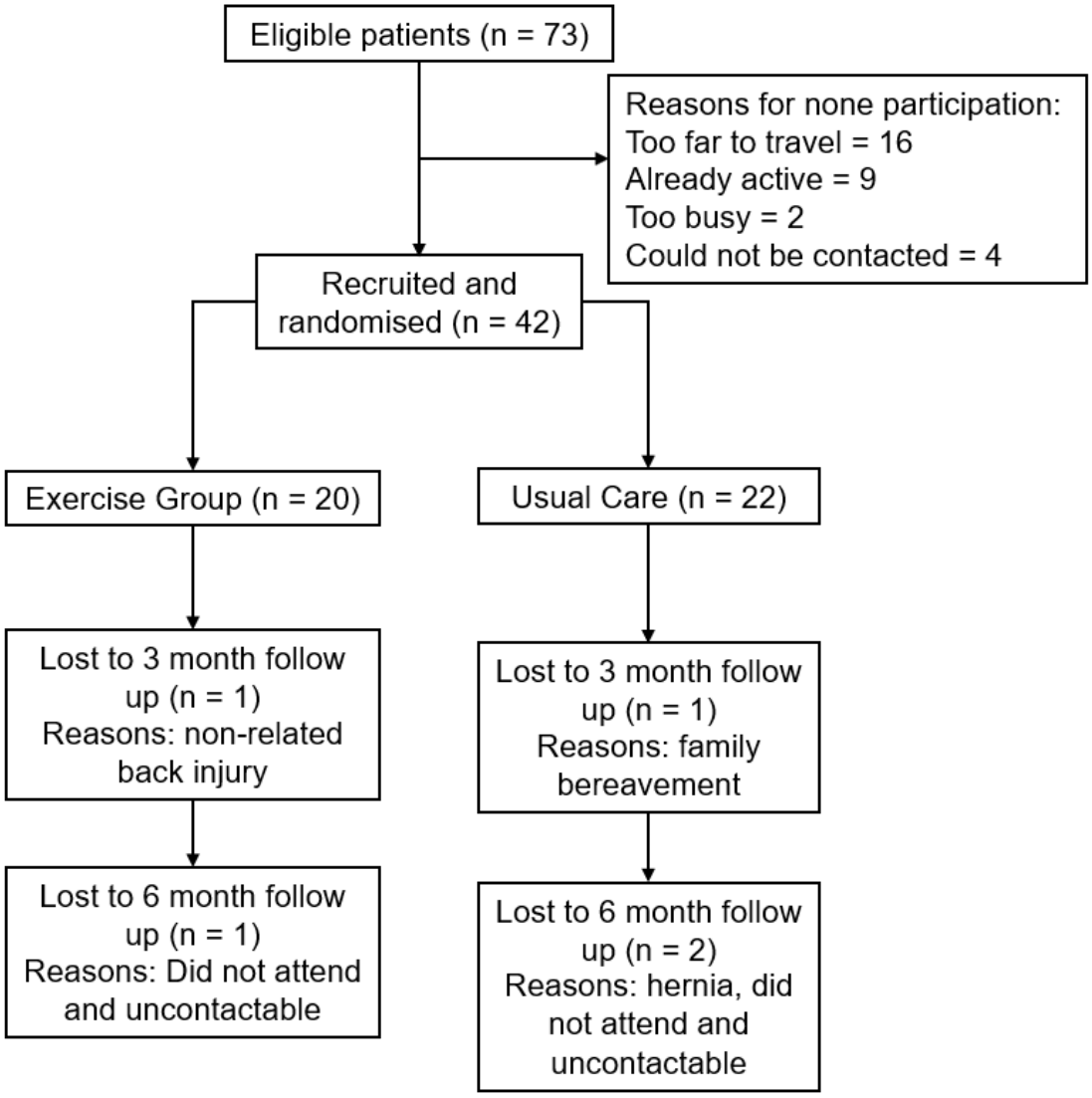

Figure 12. A flowchart of participant recruitment, randomisation, and completion.

Table 13. Patient demographics upon recruitment.

	Exercise Group (n = 20)	**Usual Care (n = 22)**
Age *(years)*	64.6 ± 6.2	66.9 ± 6.8
Stature *(cm)*	176.9 ± 7.8	175.8 ± 6.5
Body Mass *(kg)*	88.0 ± 13.3	87.6 ± 13.9
Body Mass Index *(kg/m^2)*	28.1 ± 3.5	28.3 ± 4.1
White British *(n (%))*	19 (95%)	22 (100%)
Weeks since surgery	10 ± 1	11 ± 2
Pre-operative PSA *(ng/ml)*	12.1 ± 10.9	11.9 ± 11.3
Data are presented as mean ± standard deviation unless stated otherwise. PSA – prostate specific androgen		

6.3.2 Missing Data

Missing data was evident for some variables, particularly blood biomarkers and FMD with further detail presented in Appendix 4c. Some missing data was due to participants dropping out of the study at varying time points. All participants who attended follow-up sessions had blood taken, however, approximately 15% of participants did not have some sample results returned from the laboratory or results were incomplete. Approximately 38% of participants had some missing data over the 24 weeks for FMD. This was primarily due to the unavailability of equipment, despite it being requested.

6.3.3 Intervention Adherence

Adherence to the RET intervention was generally high. In weeks 1-12 adherence was 94.1% ± 10.5%. An average of 1.9 ± 3.8 sessions were missed in the first 12 weeks. During the first 12 weeks one participant suffered a pulmonary embolism which meant they could not complete 2 weeks of the

programme. More common reasons for missing sessions were a bad back, common cold and holidays. In weeks 13-24 adherence was slightly lower at 77.7% ± 29.8%. An average of 8.0 ± 10.6 sessions were missed in weeks 13-24. Reasons provided here included becoming a father, Christmas celebrations, a rotator cuff injury and holidays with a handful of participants simply not returning the diaries for analysis.

6.3.4 Flow Mediated Dilatation

FMD outcome data are presented in Table 14. No significant differences were observed between groups at 12 or 24 weeks however some variables, at both time points, were in favour of the RET programme.

6.3.5 Blood Biomarkers

There were no significant changes to any blood biomarkers although most demonstrate a trend towards a reduction such as fasted insulin, HOMA-IR, LDL cholesterol and non-HDL cholesterol at 12 weeks and all but HDL cholesterol at 24 weeks. The mean difference and 95% confidence intervals (CI) for all blood biomarkers are present in Table 15.

Table 14. FMD outcome data at 12 and 24 weeks.

	RET Intervention			Usual Care			Adjusted mean difference between groups (95% CI)	
	Baseline	**12 Weeks**	**24 Weeks**	**Baseline**	**12 Weeks**	**24 Weeks**	**Baseline - 12 Weeks**	**Baseline - 24 Weeks**
Flow-Mediated Dilatation								
Baseline Diameter (mm)	4.9 ± 0.6	5.1 ± 0.6	4.9 ± 0.4	4.7 ± 0.6	5.1 ± 0.7	5.0 ± 0.6	-0.1 (-0.4, 0.3)	-0.1 (-0.4, 0.2)
Max Diameter (mm)	5.2 ± 0.6	5.3 ± 0.6	5.4 ± 0.4	5.1 ± 0.7	5.2 ± 0.7	5.4 ± 0.7	0.1 (-0.3, 0.5)	0.0 (-0.4, 0.3)
Recovery Diameter (mm)	5.0 ± 0.6	5.3 ± 0.5	4.9 ± 0.4	5.0 ± 0.5	5.0 ± 0.7	5.1 ± 0.6	0.3 (-0.1, 0.7)	-0.1 (-0.5, 0.2)
FMD (%)	7.4 ± 2.4	6.5 ± 2.3	7.8 ± 3.5	7.2 ± 3.4	6.5 ± 2.0	6.9 ± 3.3	-0.1 (-1.5, 1.3)	0.9 (-1.5, 3.3)
FMDr (%)	5.0 ± 2.0	3.3 ± 1.1	7.3 ± 3.9	4.0 ± 1.0	4.0 ± 2.7	5.7 ± 2.8	-0.8 (-2.3, -0.7)	1.1 (-1.4, 3.6)
Shear Baseline (s^{-1})	76.2 ± 25.1	77.0 ± 26.3	96.4 ± 46.6	81.2 ± 24.5	77.2 ± 20.7	84.2 ± 28.7	0.6 (-16.0, 17.3)	16.8 (-6.2, 39.7)
Shear Max (s^{-1})	391.2 ± 78.0	364.7 ± 64.4	387.8 ± 75.6	299.8 ± 169.5	346.8 ± 76.2	400.0 ± 110.4	17.8 (-30.1, 65.7)	-12.2 (-77.0, 52.5)
Shear Area	12465.8 ± 3231.4	13101.5 ± 4974.9	11818.1 ± 3702.8	15193.1 ± 16322.0	11688.0 ± 4020.9	13450.3 ± 6141.5	1885.0 (-1060.1, 4830.0)	-1404.8 (-4852.6, 2049.1)
Shear Area to Max	8548.4 ± 1682.8	8118.2 ± 3503.3	7320.5 ± 3444.9	8945.7 ± 5220.5	6219.2 ± 2946.8	8046.3 ± 5312.3	-1874.3 (-412.9, 5161.5)	-673.1 (-3741.5, 2395.3)

Data are presented as mean ± SD unless stated otherwise.
*indicates $P < 0.05$
N.B. on ANCOVA assumptions: (i) The normality assumption appeared to be violated for FMDr, shear baseline, shear max, area and area to max, (ii) Levene's test of homogeneity of variance was significant ($P < 0.05$) for FMDr at 12 weeks. Mann-Whitney U tests on follow-up scores produced a P value of 0.01.
FMD – flow-mediated dilatation, FMDr – flow-mediated dilatation with respect to recovery diameter, CI - confidence interval.

Table 15. Blood biomarker data at 12 and 24 weeks.

	RET Intervention			Usual Care			Adjusted mean difference between groups (95% CI)	
	Baseline	**12 Weeks**	**24 Weeks**	**Baseline**	**12 Weeks**	**24 Weeks**	**Baseline - 12 Weeks**	**Baseline - 24 Weeks**
Blood Biomarkers								
Glucose (mmol/L)	6.2 ± 1.9	5.9 ± 2.1	6.3 ± 1.6	5.4 ± 0.5	5.7 ± 0.7	6.1 ± 1.1	0.03 (-1.0, 1.0)	-0.3 (-1.1, 0.4)
Insulin (µU/ml)	103.2 ± 263.9	60.1 ± 11.0	78.3 ± 49.3	38.4 ± 21.5	75.2 ± 10.5	88.5 ± 61.3	-15.2 (-46.2, 15.9)	-10.7 (-46.7, 25.2)
HOMA-IR	2.3 ± 5.4	1.0 ± 0.8	1.2 ± 0.8	0.6 ± 0.4	1.2 ± 11.1	1.4 ± 1.1	-0.3 (-1.0, 0.3)	-0.3 (-0.9, 0.3)
Total Chol (mmol/L)	5.0 ± 1.1	4.9 ± 1.4	4.64± 1.0	5.0± 1.5	5.0 ± 1.2	4.9 ± 1.2	-0.1 (-0.6, 0.4)	-0.4 (-0.9, 0.03)
HDL (mmol/L)	1.3 ± 0.3	1.3 ± 0.2	1.2 ± 0.2	1.3 ± 0.3	1.3 ± 0.2	1.2 ± 0.2	-0.04 (-0.5, 0.4)	0.01 (-0.1, 0.1)
LDL (mmol/L)	3.2 ± 0.8	2.6 ± 0.7	2.7 ± 0.7	2.8 ± 1.2	2.6 ± 0.8	2.9 ± 0.6	-0.2 (-0.8, 0.4)	-0.3 (-0.7, 0.1)
Non-HDL (mmol/L)	3.7 ± 1.0	3.5 ± 1.3	3.2 ± 1.2	3.8 ± 1.5	3.8 ± 1.2	3.6 ± 1.1	-0.2 (-0.5, 0.003)	-0.3 (-0.9, 0.2)
Triglycerides (mmol/L)	1.5 ± 0.7	1.9 ± 1.7	1.6 ± 0.8	1.4 ± 0.6	1.7 ± 0.7	1.8 ± 0.8	0.1 (-0.6, 0.8)	-0.2 (-0.6, 0.2)
Total:HDL (mmol/L)	4.0 ± 0.9	3.8 ± 1.1	3.7 ± 1.0	4.0 ± 1.1	3.8 ± 1.0	4.0 ± 0.9	0.01 (-0.5, 0.6)	-0.2 (-0.7, 0.3)

Data are presented as mean ± SD unless stated otherwise.
*indicates $P < 0.05$
N.B. on ANCOVA assumptions: (i) The normality assumption appeared to be violated for glucose, insulin, HOMA-IR, non-HDL, triglycerides and total:HDL, (ii) Levene's test of homogeneity of variance was significant ($P < 0.05$) for the glucose and triglyceride variables at 12 weeks. Mann-Whitney U tests on follow-up scores produced P values of 0.09 and 0.09 for these variables, respectively.
HOMA-IR – insulin resistance, Chol – cholesterol, HDL – high density lipoprotein cholesterol, LDL – low density lipoprotein cholesterol ANCOVA - analysis of covariance, CI - confidence interval.

6.3.6 Cardiovascular Heath

At 12 weeks, the RET groups did not demonstrated any significant reductions in cardiovascular health variables when compared to the usual care group although SBP and MAP showed a reduction in favour of RET at 12 and 24 weeks (Table 16). No changes were evident in DBP, heart rate or QRisk2 score at either time point.

6.3.7 Anthropometric Profile

Changes to body composition were evident in the RET group both at 12 and 24 weeks (Table 16). Significant reductions were observed in the RET group compared to usual care in the sum of 6 skinfolds (-1.9 [-3.4, -0.4] mm, P = 0.014) at 12 weeks. At 24 weeks body mass (-3.1 [-6.0, -0.2] kg, P = 0.036), BMI (-1.0 [-1.9, -0.1] kg/m^2, P = 0.034), fat percentage (-1.9 [-3.5, -0.4] %, P = 0.017) and sum of 8 skinfold (-13.3 [-25.3, -1.4] mm, P = 0.029) variables showed significant reductions for those in the RET group when compared to usual care.

6.3.8 Submaximal Aerobic Capacity

The mean difference and 95% CI for the submaximal aerobic capacity test are presented in Table 17. When compared to usual care, RET demonstrated significant increases in all submaximal aerobic capacity variables apart from maximum heart rate at both 12 and 24 weeks.

6.3.9 Strength

Significant changes are observed in the RET group for upper body strength at 12 (3.6 [1.7, 5.5] reps, P < 0.001) and 24 weeks (4.3 [1.2, 7.3] reps, P = 0.008; Table 17). Increases to lower body strength were also demonstrated at 12 (3.1 [1.0, 5.2] reps, P = 0.004) and 24 (3.2 [0.6, 5.9] reps, P = 0.019) weeks for the RET group compared to usual care.

Table 16. Cardiovascular health data and anthropometric profile at 12 and 24 weeks.

	RET Intervention			Usual Care			Adjusted mean difference between groups (95% CI)	
	Baseline	**12 Weeks**	**24 Weeks**	**Baseline**	**12 Weeks**	**24 Weeks**	**Baseline - 12 Weeks**	**Baseline - 24 Weeks**
Cardiovascular Health								
Resting Heart Rate (bpm)	71.7 ± 12.5	72.0 ± 10.3	75.6 ± 11.4	66.8 ± 9.3	68.7 ± 10.1	72.4 ± 10.6	0.9 (-4.7, 6.5)	0.7 (-5.7, 7.1)
SBP (mmHg)	137.6 ± 17.2	132.1 ± 16.7	133.0 ± 19.1	135.5 ± 14.6	136.1 ± 12.5	137.9 ± 14.5	-5.5 (-11.5, 0.6)	-6.6 (-15.1, 1.9)
DBP (mmHg)	81.9 ± 12.6	80.2 ± 7.5	82.6 ± 10.6	82.0 ± 9.4	81.3 ± 7.7	81.5 ± 8.4	-1.0 (-5.3, 3.2)	1.0 (-4.6, 6.7)
MAP (mmHg)	100.4 ± 11.5	97.7 ± 9.7	99.5 ± 12.8	99.8 ± 10.3	99.6 ± 8.2	100.3 ± 9.3	-2.2 (-6.5, 2.1)	-1.1 (-7.3, 5.1)
QRisk-2 Score (%)	17.0 ± 7.7	16.87± 7.2	16.6 ± 6.3	18.0 ± 6.8	17.4 ± 7.0	16.9 ± 6.5	0.1 (-2.7, 2.9)	0.3 (-2.7, 3.2)
Anthropometric Profile								
Body Mass (kg)	88.0 ± 13.3	87.3 ± 13.8	85.9 ± 14.0	87.6 ± 13.9	88.2 ± 14.4	88.5 ± 14.3	-1.4 (-3.6, 0.6)	-3.1 (-6.0, -0.2)*
BMI (kg/m^2)	28.1 ± 3.5	27.8 ± 3.4	27.6 ± 3.5	28.3 ± 4.1	28.5 ± 4.2	28.8 ± 4.5	-0.4 (-1.1, 0.2)	-1.0 (-1.9, -0.1)*
Waist Circumference (cm)	99.6 ± 10.0	98.6 ± 9.3	98.9 ± 9.4	103.0 ± 9.7	102.7 ± 9.0	104.1 ± 9.4	-1.3 (-3.9, 1.3)	-2.3 (-5.1, 0.5)
Waist:Hip	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.0 (0.0, 0.0)	-0.03 (-0.1, 0.006)
Fat (%)	18.3 ± 4.0	16.8 ± 3.0	16.6 ± 3.2	17.9 ± 4.6	18.3 ± 4.8	18.2 ± 4.6	-13.2 (-26.8, 0.4)	-1.9 (-3.5, -0.4)*
Sum of 6 Skinfolds (mm)	103.9 ± 24.5	95.1 ± 19.8	92.5 ± 19.0	101.2 ± 27.0	106.4 ± 33.7	98.7 ± 27.4	-1.9 (-3.4, -0.4)*	-8.2 (-17.1, 0.6)
Sum of 8 Skinfolds (mm)	135.6 ± 29.2	124.2 ± 24.1	118.2 ± 24.2	132.8 ± 34.6	134.6 ± 35.7	129.5 ± 34.0	-12.4 (-25.9, 1.1)	-13.3 (-25.3, -1.4)*

Data are presented as mean ± SD unless stated otherwise.
*indicates $P < 0.05$
N.B. on ANCOVA assumptions: (i) The normality assumption appeared to be violated for Body Mass, BMI, Fat % and Sum of 6 at 12 weeks and Body Mass, SBP and Q-Risk 2 at 24 weeks (ii) Levene's test of homogeneity of variance was significant ($P < 0.05$) for BMI, Fat %, Sum of 6 and QRisk-2 variables at 12 weeks. Mann-Whitney U tests on follow-up scores produced P values of 0.7, 0.2, 0.3, and 0.9 for these variables, respectively.
BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure, CI - confidence interval.

Table 17. Submaximal aerobic capacity and strength data at 12 and 24 weeks.

	RET Intervention			Usual Care			Adjusted mean difference between groups (95% CI)	
	Baseline	**12 Weeks**	**24 Weeks**	**Baseline**	**12 Weeks**	**24 Weeks**	**Baseline - 12 Weeks**	**Baseline - 24 Weeks**
Submaximal Aerobic Exercise								
Stage	30.0 ± 11.4	36.3 ± 11.4	39.5 ± 10.2	29.8 ± 10.3	28.8 ± 12.0	32.5 ± 10.7	7.3 (3.0, 11.6)*	6.8 (2.4, 11.1)*
Time (secs)	580.0 ± 229.0	703.4 ± 228.1	774.9 ± 200.7	575.5 ± 205.4	556.1 ± 241.9	631.8 ± 214.4	142.3 (55.2, 231.5)*	139.8 (53.9, 225.7)*
Estimated VO_2max (ml/kg/min)	38.6 ± 13.8	45.6 ±12.8	49.7 ± 11.4	38.7 ± 12.5	37.8 ± 14.3	41.2 ± 12.9	7.8 (3.2, 12.5)*	8.5 (3.8, 13.1)*
Estimated METs	11.0 ± 3.9	12.7 ± 4.0	14.2 ± 3.3	11.0 ± 3.4	10.8 ± 4.1	11.8 ± 3.7	1.9 (0.3, 3.4)*	2.3 (0.9, 3.8)*
Max HR (bpm)	143.2 ± 17.3	139.8 ± 17.3	146.2 ± 14.6	132.9 ± 17.3	127.9 ± 17.2	134.1 ± 13.7	3.1 (-2.8, 9.1)	6.8 (-0.8, 14.4)
Strength								
Upper Body (reps)	20.0 ± 5.7	24.6 ± 5.8	27.2 ± 7.3	19.4 ± 4.2	20.5 ± 4.3	22.5 ± 4.7	3.6 (1.7, 5.5)*	4.3 (1.2, 7.3)*
Lower Body (reps)	17.9 ± 5.1	22.3 ± 6.2	24.4 ± 6.4	16.1 ± 5.3	17.4 ± 5.9	19.7 ± 5.9	3.1 (1.0, 5.2)*	3.2 (0.6, 5.9)*

Data are presented as mean ± SD unless stated otherwise.
*indicates $P < 0.05$
N.B. on ANCOVA assumptions: (i) The normality assumption appeared to be violated for Lower Body Strength at 12 weeks and Max HR, Upper Body Strength and Lower Body Strength at 24 weeks.
VO_2Peak – maximal aerobic capacity, METs – metabolic equivalent, HR – heart Rate, reps – repetitions, secs – seconds, CI - confidence interval.

6.3.10 Questionnaires

All questionnaire data is presented in Table 18. No statistical differences were evident in EQ-5D index score or the VAS at 12 or 24 weeks.

The RET group demonstrated significant changes to the functional wellbeing (1.9 [0.3, 3.5], *P* = 0.02), prostate cancer specific (2.3 [1.0, 3.7], *P* = 0.001, trial outcome index (5.0 [1.9, 9.1], *P* = 0.002) and the FACT-P total score (5.3 [0.7, 9.8], *P* = 0.03) elements of the FACT-P at 12 weeks. At 24 weeks, significant changes were also present for functional wellbeing (1.9 [0.001, 3.8], *P* = 0.05), prostate cancer specific (3.1 [1.3, 5.0], *P* = 0.002) and the trial outcome index (5.0 [1.8, 8.3], *P* = 0.003).

At 12 weeks there were significant differences observed for RET compared to usual care for moderate intensity aerobic activity duration (22.1 [4.1, 40.0] mins, *P* = 0.02) but not for the frequency of the activity (0.2 ([-1.2, 1.6], *P* = 0.8). Expectedly, there was a significant difference in the frequency and duration of RET at both 12 and 14 weeks for the RET group compared to the usual care group. There were no differences in the other exercise intensities at 24 weeks.

There were no changes observed in the BFI scores at either 12 or 24 weeks.

Table 18. Questionnaire data for 12 and 24 weeks.

	RET Intervention			Usual Care			Adjusted mean difference between groups (95% CI)	
	Baseline	**12 Weeks**	**24 Weeks**	**Baseline**	**12 Weeks**	**24 Weeks**	**Baseline - 12 Weeks**	**Baseline - 24 Weeks**
Quality of Life								
EQ-5D Index Score	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.2	0.9 ± 0.1	0.8 ± 0.2	0.02 (-0.04, 0.1)	0.1 (-0.01, 0.1)
ED-5D VAS	81.5 ± 12.6	83.7 ± 10.1	83.9 ± 9.8	77.6 ± 13.5	80.6 ± 11.3	83.2 ± 8.9	1.2 (-4.3, 6.7)	-0.7 (-5.8, 4.3)
FACT-P								
Physical WB	25.4 ± 1.8	26.3 ± 1.4	26.1 ± 1.5	24.3 ± 2.9	24.7 ± 3.2	25.12± 2.9	0.8 (-0.4, 2.0)	0.2 (-0.9, 1.3)
Social WB	23.4 ± 3.5	23.5 ± 2.7	23.3 ± 3.4	22.5 ± 3.6	21.9 ± 3.3	25.6 ±12.3	1.2 (-0.4, 2.8)	-2.4 (-8.3, 3.5)
Emotional WB	21.6 ± 2.4	21.2 ± 3.2	21.9 ± 1.8	20.8 ± 3.7	21.3 ± 3.2	20.2 ± 3.8	-0.7 (-1.9, 0.6)	1.1 (-0.1, 2.3)
Functional WB	21.5 ± 5.2	23.8 ± 3.6	24.2 ± 3.1	21.2 ± 5.5	21.7 ± 4.3	22.2 ± 4.9	1.9 (0.3, 3.5)*	1.9 (0.01, 3.8)*
Prostate Cancer Specific	34.5 ± 3.2	39.1 ± 2.2	40.5 ± 2.4	33.3 ± 5.2	36.1 ± 4.0	36.7 ± 4.5	2.3 (1.0, 3.7)*	3.1 (1.3, 5.0)*
FACT-P TOI	81.4 ± 8.7	89.2 ± 6.2	90.9 ± 5.4	78.8 ± 11.5	82.5 ±10.2	84.1 ± 10.6	5.0 (1.9, 9.1)*	5.0 (1.8, 8.3)*
FACT-P Total Score	126.4 ± 12.1	133.8 ± 9.5	136.0 ± 8.0	122.1 ± 16.2	125.6 ± 14.2	129.8 ± 13.6	5.3 (0.7, 9.8)*	4.2 (-1.6, 10.1)
FACT-G Total Score	91.9 ± 10.0	94.8 ± 8.1	95.5 ± 6.7	88.8 ± 12.1	89.5 ± 11.4	93.3 ± 10.6	3.1 (-0.8, 7.0)	0.9 (-4.0, 5.7)
Fatigue								
BFI	1.2 ± 1.2	1.3 ± 1.1	1.4 ± 1.2	1.9 ± 1.4	2.0 ± 1.8	1.6 ± 1.5	-0.5 (-1.3, 0.3)	-0.1 (-0.9, 0.6)

Table 18. Continued.

	RET Intervention			Usual Care			Adjusted mean difference between groups (95% CI)	
	Baseline	**12 Weeks**	**24 Weeks**	**Baseline**	**12 Weeks**	**24 Weeks**	**Baseline - 12 Weeks**	**Baseline - 24 Weeks**
Godin Leisure Time Exercise Questionnaire (modified)								
VA Frequency (days/week)	0.0 ± 0.0	0.4 ± 1.1	0.6 ± 1.1	0.4 ± 1.5	0.3 ± 0.6	0.3 ± 0.4	0.1 (-0.4, 0.7)	0.4 (-0.1, 0.9)
VA Duration (mins/session)	0.0 ± 0.0	3.1 ± 8.0	6.4 ± 12.7	1.1 ± 3.8	27.7 ± 83.5	10.1 ± 20.1	-27.2 (-66.3, 11.9)	-3.2 (-14.2, 7.8)
MIA Frequency (days/week)	1.8 ± 2.8	2.8 ± 2.2	1.8 ± 1.9	1.0 ± 2.0	2.2 ± 2.6	1.4 ± 2.0	0.2 (-1.2, 1.6)	0.3 (-0.9, 1.5)
MIA Duration (mins/session)	15.9 ± 27.6	39.4 ± 34.9	39.7 ± 47.0	25.7 ± 56.5	18.5 ± 21.6	22.9 ± 30.8	22.1 (4.1, 40.0)*	16.9 (-8.1, 42.0)
LIA Frequency (days/week)	4.6 ± 2.2	3.1 ± 2.5	2.6 ± 2.4	5.3 ± 2.6	4.5 ± 2.5	3.6 ± 2.7	-1.0 (-2.4, 0.4)	-0.7 (-2.2, 0.8)
LIA Duration (mins/session)	40.0 ± 31.5	29.5 ± 28.2	41.2 ± 44.4	59.6 ± 61.4	49.9 ± 55.2	52.3 ± 65.0	-10.4 (-33.9, 13.2)	3.4 (-24.1, 30.9)
RET Frequency (days/week)	0.4 ± 1.6	3.3 ± 1.0	3.0 ± 1.7	0.5 ± 1.6	0.7 ± 1.7	1.1 ± 1.6	2.6 (1.8, 3.5)*	1.9 (1.0, 2.9)*
RET Duration (mins/session)	0.5 ± 2.2	32.9 ± 10.8	22.6 ± 12.4	2.5 ± 9.7	6.0 ± 12.4	6.4 ± 9.8	27.8 (20.7, 35.0)*	17.4 (10.8, 24.0)*

Data are presented as mean ± SD unless stated otherwise.
*indicates $P < 0.05$
N.B. on ANCOVA assumptions: (i) The normality assumption appeared to be violated for EQ-5D VAS, Physical WB, Social WB, VA frequency and duration, MIA frequency and duration, LIA frequency and duration, RET frequency and duration for 12 weeks. The normality assumption was also violated at 24 weeks for Physical WB, Social WB, Functional WB, FACT-P Total Score, FACT-G Total Score, BFI, VA frequency and duration, MIA frequency and duration, LIA frequency and duration, RET frequency and duration, (ii) Levene's test of homogeneity of variance was significant ($P < 0.05$) for the VA duration at 12 weeks and VA frequency and Emotional WB at 24 weeks. Mann-Whitney U tests on follow-up scores produced P values of 0.3, 0.8 and 0.2 for all these variables.
VAS – visual analogue scale, WB – Well-being, TOI – trial outcome index, VA - vigorous aerobic activity, MIA – moderate intensity aerobic activity, LIA – low intensity aerobic activity, RET – resistance exercise training, ANCOVA - analysis of covariance, CI - confidence interval.

6.3.11 Adverse Events

Five non-serious adverse events (hernia, accident resulting in back pain, abdominal pain, increased fasted insulin level, rotator cuff injury) and one serious adverse event (pulmonary embolism) were reported throughout the trial duration. Only the report of a rotator cuff injury was related to the trial and was the result of a participant choosing to progress to a more difficult resistance band despite being told not to. This participant was referred for physiotherapy and continued with the exercise programme but did not complete any exercises which the physiotherapist deemed would aggravate the injury.

6.4 Discussion

This is the first study to our knowledge to explore the benefits of RET in men who have undergone robot-assisted radical prostatectomy in the previous 8-12 weeks. This study demonstrates that RET after robot-assisted radical prostatectomy can positively impact upon some aspects of body composition, strength, $\dot{V}O_2$Peak and patient-reported side effects of the treatment in the 8 months post-surgery. Additionally, due to the low number of adverse events and good adherence levels throughout the intervention, it is reasonable to suggest that RET is a safe and effective form of exercise in the months following robot-assisted radical prostatectomy.

FMD is calculated as the greatest percent change in arterial diameter following arterial occlusion and some favourable changes were observed during this study for FMD in the RET group. A recent review of FMD analysis methods highlight some issues with using allometric scaling of FMD in clinical trials, such as the difficulties in using the method to establish clinically meaningful difference in FMD, therefore this was not performed (McLay, Nederveen, Koval, Paterson, & Murias, 2018). Albeit not significant, this study observed increases in maximum diameter and baseline shear rate in the RET group at 12 weeks. Artery dilation during the FMD response is thought to be due to shear rate stimulating the release of vasoactive substances which go on to act

on vascular smooth muscle (Cangemi et al., 2018; Thijssen, 2011). Furthermore, at 24 weeks there were also non-significant improvements evident in FMD and FMDr. The chronic effects of aerobic exercise training have been shown to improve endothelial function in populations with high CVD risk and prevent the age-associated loss in endothelium dependent vasodilation in men (DeSouza et al., 2000) However, the majority of studies examining endothelial function after RET only investigate the acute effects of a single bout of RET (Francois, Durrer, Pistawka, Halperin, & Little, 2016; Morishima, Tsuchiya, Iemitsu, & Ochi, 2018).

The differences observed here are not as great as expected for patients taking part in an RET programme. Other studies have reported a change in FMD from 6.2-8.3% and 9.7-11.8% after resistance-based exercise programmes however these were in young (18-35 years old) prehypertensives and healthy young (18 years old) adults respectively (Beck, Casey, Martin, Emerson, & Braith, 2013; Okamoto, Masuhara, & Ikuta, 2011). The lack of statistical significance here is likely to be due to the study being underpowered, as it was estimated 60 participants were needed to potentially observe significant differences in FMD. However, to our knowledge this is the first study to examine endothelial function after 24 weeks RET in prostate cancer patients treated with robot-assisted radical prostatectomy and therefore further studies are needed to explore this further.

At baseline, resting heart rate was low and within normal limits in both the RET and usual care groups and so no change in this variable is not surprising. However, systolic blood pressure and mean arterial pressure demonstrated favourable reductions over 12 and 24 weeks for the RET group. This is a potentially important finding given that approximately half of all myocardial infarctions in the UK are attributed to hypertension and as cardiovascular disease has been identified as one of the leading causes of death in men following robot-assisted radical prostatectomy (Public Health England, 2017; Shikanov, Kocherginsky, Shalhav, & Eggener, 2011; World Health Organisation, 2009). Therefore, RET could be utilised in men after robot-assisted radical prostatectomy as a non-pharmacological method of reducing arterial blood pressure.

Aerobic capacity is known to decline with increasing age and with diagnosed hypertension therefore older adults exert themselves more conducting activities of daily living compared to younger adults. Such decreases in $\dot{V}O_2$Peak can not only aggravate underlying cardiovascular conditions, but it can also reduce activities of daily living and increase the risk of depression and functional dependence (Chandrasekaran et al., 2010). Submaximal exercise testing is a means of predicting $\dot{V}O_2$Peak without performing maximal exercise and is often associated with fewer risks for clinical populations. Aerobic exercise has traditionally been employed to improve $\dot{V}O_2$Peak (Chodzko-Zajko, 2009), however, the results in this study show that RET can improve submaximal exercise performance and therefore helping to combat the age-related declines in $\dot{V}O_2$Peak.

With the age of those recruited in this study being > 60 years of age, it is possible that some of those who took part were experiencing age related declines in muscle mass and function (i.e. sarcopenia) (Dodds & Sayer, 2016). However, as with the majority of RET programmes we observed a significant increase in upper and lower body strength in the RET group compared to usual care. Furthermore, there were significant changes in all body composition variables for the RET group over the 24 weeks. The observed changes in body composition and reduction in fat mass supports suggestions that RET is beneficial in promoting fat loss (A. Paoli, Gentil, Moro, Marcolin, & Bianco, 2017; Antonio Paoli, Moro, & Bianco, 2015; Willis et al., 2012). The findings here are in agreement with other studies that have also reported favourable changes in body composition following periods of RET (Padilha et al., 2017; Shaw, Gouveia, McIntyre, & Shaw, 2016; Villanueva, Lane, & Schroeder, 2015). Such effects are potentially attributable to training intensity since some studies have shown increases in basal metabolic rates and fat oxidation following RET (Alvehus, Boman, Söderlund, Svensson, & Burén, 2014; Lemmer et al., 2001).

There was no beneficial effect observed for fatigue levels in the RET group. This could be due to the relatively low levels of fatigue reported by participants at baseline. However, other studies have found exercise to reduce the levels of fatigue in other cancer populations (Meneses-Echavez et al., 2015).

Furthermore, the study was underpowered to detect any potentially small but important differences in the questionnaire outcome. The beneficial effects of RET were evident in the improvement of elements of the FACT-P questionnaire. The results suggest that RET can improve patient-reported functional wellbeing and prostate cancer specific factors such as urinary incontinence and frequency, and erectile dysfunction. Such factors are known to improve over the months after surgery however, the significant difference between the two groups suggests that RET could be more beneficial than usual care (Ernstmann, Weissbach, Herden, Winter, & Ansmann, 2017). This potentially has clinical implications to the advice and recommendations clinicians make to patients at this stage of their recovery.

6.4.1 Limitations

It is important to interpret these results in the context of several limitations. Firstly, there are issues surrounding studies being underpowered. For example, the risk of false negatives is greater and inflated effects sizes are more common (Button et al., 2013). However, significant beneficial effects were evident for some of the secondary outcomes (i.e. waist circumference, strength, $\dot{V}O_2$Peak and elements of the FACT-P). Furthermore, there are issues with imputing missing data despite missing data being common in clinical research. Missing data points can lead to a loss in statistical power and potentially biased results if not handled appropriately. However, multiple imputation was employed which is widely adopted in practice for dealing with missing data (Hayati Rezvan et al., 2015).

It is possible that, due to patients being aware of their participation in an exercise trial, they undertook more daily exercise accounting for the increased duration of moderate intensity aerobic activity in the RET group at 12 weeks. This could have contributed to an increase in Bruce ramp scores, however as there are no differences at the 24-week time-point it is unlikely that this is a contributing factor. Moreover, diet may also have changed due to participation in the trial, which was not accounted for, this may have led to favourable reductions in body/fat mass.

6.5 Conclusions

This study highlights that RET is a safe and effective mode of exercise that elicits numerous cardiometabolic health benefits in men who have undergone robot-assisted radical prostatectomy. RET had a clear effect on body composition, $\dot{V}O_2$Peak, strength, functional wellbeing and prostate cancer specific quality of life and showed evidence of a favourable reduction in MAP, SBP, HOMA-IR, LDL cholesterol. The RET programme was well received by patients with adherence to the programme over 90% in the initial 12 weeks. Clinicians should consider discussing the benefits of exercise, particularly RET, to patients in the weeks following robot-assisted radical prostatectomy. Future studies should expand on this trial and explore these variables in a larger multi-centre randomised controlled trial.

CHAPTER 7

GENERAL DISCUSSION AND CONCLUSION

7.0 General Discussion and Conclusion

7.1 Introduction

The research presented in this thesis has systematically examined evidence for the benefits of RET in both healthy adults and those at elevated cardiometabolic risk. In addition, the relationship between self-reported physical activity and fatigue in men receiving treatment for prostate cancer was examined. The effects of a supported, home-based RET programme in men after robot-assisted radical prostatectomy was the investigated in a randomised controlled trial. This chapter will collate and consider the findings of chapters 3 to 6.

7.2 Summary of Key Findings

The systematic review described in Chapter 3 identified the effects of RET versus control conditions in adults, as well as the strengths and limitations of existing studies. This systematic review demonstrated that an RET programme can elicit improvements in resting blood pressure, FMD, HOMA-IR, fasted glucose, insulin and $\dot{V}O_2$Peak, with most of the evidence available for interventions 7-23 weeks in duration. It was concluded that RET is a safe and effective exercise modality for inducing improvements cardiometabolic risk factors and cardiopulmonary fitness, particularly in middle-aged to older adults (≥ 41 years) and those with elevated cardiometabolic risk or disease. However, there was some uncertainty regarding the risk of bias because very few studies adequately reported the randomisation process, allocation concealment or blinding of outcome assessment. Additionally, many studies did not follow the TIDieR checklist (Hoffmann et al., 2014) and so had incomplete descriptions of the RET interventions, progression and adherence.

Moreover, a pilot study was conducted to characterise fatigue, physical activity levels and cardiovascular status, in men after robot-assisted radical prostatectomy (Chapter 4). This study demonstrated that some men following

robot-assisted radical prostatectomy are at increased risk of clinically significant consequences from cardiovascular disease within ten years of their surgery and a substantial proportaion do suffer with clinically significant levels of fatigue. This suggests that patients due to receive robot-assisted radical prostatectomy as a treatment for prostate cancer should be counselled by the clinician on these factors. The research has shown that men after robot-assisted radical prostatectomy appear to meet the recommended guidelines for aerobic physical activity but do not meet them for resistance-based exercise.

A randomised controlled trial was then conducted to assess the effects of supported home-based progressive RET on cardiometabolic health outcomes following robot-assisted radical prostatectomy (Chapter 6). The men in the RET group showed improvements in endothelial function, total cholesterol, SBP, body composition, strength, $\dot{V}O_2$Peak and patient-reported functional wellbeing and prostate cancer specific quality of life. The RET intervention was also safe for patients following radical prostatectomy, with only one non-serious adverse event being related to the intervention itself. The RET programme was well accepted by patients with adherence levels greater than 90% in the first 12 weeks.

Exercise is generally recommended to men with prostate cancer (specifically men who receive ADT, radiotherapy or chemotherapy) however, there is a lack of evidence for robot-assisted radical prostatectomy population. As discussed in Chapter 6, aside from its positive impact on cardiometabolic health outcomes, RET potentially facilitates the reduction of robot-assisted radical prostatectomy specific side effects such as urinary incontinence and erectile dysfunction as assessed via the FACT-P. Although this thesis did not compare different modes of RET, it is evident, from the results presented in this thesis, that RET could be a beneficial adjunct treatment for men who receive surgical treatment for prostate cancer. Furthermore, the behaviour change techniques employed, i.e. goal setting and self-monitoring, resulted in high adherence levels and low drop-out rates for an exercise intervention study. Supported home-based RET using Therabands is a cheap, accessible and practical mode of exercise. While more research is clearly needed in the area of exercise

training for prostate cancer patients on varying treatment pathways, this study is the first to demonstrate the benefits of RET in a robot-assisted radical prostatectomy cohort.

7.3 Implications for Clinical Practice

Recently NHS England published the NHS Long Term Plan for the next 10 years. By 2028 the plan aims to improve early detection of cancer and improve survival rates (NHS England, 2019). This has the potential to increase the rates of men diagnosed with prostate cancer and improve survival from the disease, therefore meaning more men will suffer from the side effects of the treatment received. This thesis has demonstrated that men after robot-assisted radical prostatectomy who are supported through at least 12 weeks of a RET intervention report improved cardiometabolic health, functional well-being and prostate cancer specific factors (i.e. erectile dysfunction and urinary incontinence).

The results from this thesis suggest that exercise, specifically RET, should be recommended to prostate cancer patients, regardless of the type of disease or treatment pathway, to improve cardiometabolic health and in robot-assisted radical prostatectomy patients specifically, prostate cancer specific quality of life. At present, NICE only recommends exercise to prostate cancer patients, regardless of the type of treatment they received, rather than providing specific guidelines for patients to adhere to. However, this thesis has highlighted the lack of RET undertaken in this population of prostate cancer patients and so clinicians and health care professionals should provide some exercise advice as part of the initial treatment for all patients being treated via robot-assisted radical prostatectomy.

Cancer diagnosis has been described as a teachable moment in a pateints life where they are motivated to reduce unhealthy behaviours, especially when the advice is delivered by a trusted source such as a health care professional (Horwood et al., 2014; McBride et al., 2003; Sutton et al., 2017). Cumulative findings from exercise trials support the promotion of exercise principles to

gain and maintain physiological, functional, and quality of life benefits before, during and after treatment for cancer (Campbell, Stevinson, & Crank, 2012; Hayes, Spence, Galvão, & Newton, 2009; Schmitz, 2010). It is important that such programmes are tailored to individual patients taking into account their goals, strengths and weaknesses. Therefore a one-size-fits-all approach is not appropriate in this patient group or within the NHS setting. Evidence also supports using behaviour change strategies to improve exercise self-efficacy to empower people with cancer, to ensure that activity changes and subsequent benefits can be sustained (Bourke et al., 2013; Turner et al., 2018). In addition to gaining the benefits from exercise during cancer treatment, there is also preliminary evidence that exercise performed post-diagnosis may be associated with improved survival, however more research is needed (Campbell et al., 2012; Kenfield et al., 2011). Collectively, this evidence provides sound justification for including exercise as part of routine NHS cancer care. Due to resource constraints visible in the current NHS system, it is possible that remote support for home-based exercise interventions, similar to that which has been investigated in this thesis, may be a viable option for the NHS to employ.

7.4 Limitations

Specific limitations are addressed in respective chapters. The findings within this thesis are based upon a series of studies all involving a relatively small group of patients from one NHS Trust and, for this reason, the results require careful interpretation.

A further limitation is that this thesis is based upon one mode of exercise. Specific health benefits in prostate cancer patients are likely to differ across exercise modalities and intensities, and it would therefore be inappropriate to generalise these findings to other exercise modalities. Nevertheless, these limitations should not detract from the potential clinical importance of these findings as clinicians can refine consultations based patient characteristics and exercise preferences.

There were issues with the use of the SPAQ questionnaire in Chapter 4. Many patients did not fully understand the format of the questionnaire (e.g. to only include MVPA), which possibly led to over-reporting of some items, particularly walking. Therefore, the Godin Leisure Time Questionnaire (modified) was used in the randomised controlled trial (Chapter 6) as this was much simpler in layout and quicker to complete.

As with most clinical trials, recruitment was challenging, particularly for the randomised controlled trial (Chapter 6). This was in part due to time constraints but also attributable to the very large catchment area of the Trust. Many patients travelled > 2 hours to attend an outpatient appoint and did not feel that it would be beneficial for them to participate in a trial that required further trips to the hospital. However, many did comment that they would have taken part if it was ‘closer to home’.

7.5 Areas for Future Research

The next stage of research following this thesis should be extended to patient groups, urology specialists and physiotherapists/exercise physiologists to provide further guidance and refinement of the intervention components and the implementation within the care pathway. Moreover, it would be advantageous to follow on from this body of work by investigating the cost effectiveness to support the implementation of this within the NHS on a much larger scale through an appropriately design multi-centre randomised controlled trial.

Although a relatively broad ranging and comprehensive assessment of the benefits of the RET intervention was conducted, due to financial resources, it was only possible to measure a limited number of blood-borne biomarkers (lipid profile, glucose and insulin). It would therefore be of interest, and potential importance to include further blood biomarkers such as CRP and HbA1c, as well as specific questionnaires directly assessing erectile dysfunction and urinary incontinence within this population. Longer-term follow-ups (> 6 months) could also be conducted to examine whether the

improvements made in the initial 6 months of the study are maintained over a longer duration.

It is suggested that the recommendations generated from this thesis be advertised in outpatient clinics and promoted to patients who receive robot-assisted radical prostatectomy. An assessment of patient uptake on the basis of recommendations may be beneficial to assess whether providing recommendations alone is effective in provoking change in exercise behaviours.

7.6 Conclusions

The findings in this thesis have demonstrated that:

- RET of varying durations can positively impact cardiometabolic health in adults both with, and without, cardiometabolic risk factors.
- Some men after robot-assisted radical prostatectomy are at increased risk of clinically significant consequences from CVD within ten years of their surgery and suffer clinically significant levels of fatigue.
- Men using self-reported physical activity questionnaires after robot-assisted radical prostatectomy report meeting UK guidelines for aerobic activity but not resistance-based exercise.
- RET of 12-24 weeks in length elicits improvements in endothelial function, body composition, total cholesterol, SBP, $\dot{V}O_2$Peak, strength, functional wellbeing and prostate cancer specific quality of life.
- RET is a safe and effective mode of exercise for men > 8 weeks post robot-assisted radical prostatectomy and is well received by patients with adherence to the programme over 90% in the initial 12 weeks.
- Exercise should be integrated into the cancer care pathway for patients before, during and after treatment to gain and maintain physical, functional and quality of life benefits.

CHAPTER 8

APPENDICES

8.0 List of Appendices

Appendix 1 – Ethical Approvals

a) Health Research Authority Approval
b) NHS Research Ethics Committee Approval
c) Local Research and Development Approval

Appendix 2 – Chapter 3

a) Systematic Review Search Strategy
b) Trials Characteristics Included in the Systematic Review
c) Populations used in the Included Studies
d) Risk of Bias Assessment
e) Publication Bias
f) Sensitivity Analysis of the short- (ST), medium- (MT) and long-term (LT) effects of RET on cardiometabolic outcomes.
g) Short-, Medium-, Long-term Effects of Resistance Exercise Training on Study Outcomes
h) Subgroup Analysis

Appendix 3 – Chapter 6

a) Discussion Schedule Discussion Schedule
b) Exercise Manual
c) OMNI-RES RPE Scale

Appendix 4 – Chapter 7

a) Elements of the Senior Fitness Test used in the Trial
b) Questionnaire Booklet
c) Missing Data

Appendix 1a. *Health Research Authority Approval*

NHS
Health Research Authority

Professor John Saxton
Department of Sport, Exercise and Rehabilitation
City Campus
Newcastle upon Tyne
NE1 8ST

Email: hra.approval@nhs.net

14 September 2016

Dear Professor Saxton,

Letter of HRA Approval

Study title:	**Supported progressive resistance exercise for countering the adverse side effects of prostate cancer treatment**
IRAS project ID:	**202404**
REC reference:	**16/SS/0143**
Sponsor	**Northumbria University**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details

and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

IRAS project ID	202404

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **202404**. Please quote this on all correspondence.

Yours sincerely

Thomas Fairman
HRA Assessor

Email: hra.approval@nhs.net

Copy to: *Mrs Samantha King, Northumbria University, (Sponsor Contact)*
Ms Susan Ridge, Newcastle Joint Research Office, (Lead NHS R&D Contact)

Appendix 1b. *NHS Research Ethics Committee Approval*

Lothian NHS Board

South East Scotland Research
Ethics Committee 02

Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG
Telephone 0131 536 9000

www.nhslothian.scot.nhs.uk

Date 08 September 2016
Your Ref
Our Ref

Enquiries to: Joyce Clearie
Extension: 35674
Direct Line: 0131 465 5674
Email: Joyce.Clearie@nhslothian.scot.nhs.uk

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

08 September 2016

Professor John Saxton
Department of Sport, Exercise and Rehabilitation
City Campus
Newcastle upon Tyne
NE1 8ST

Dear Professor Saxton

Study title: **Supported progressive resistance exercise for countering the adverse side effects of prostate cancer treatment**
REC reference: **16/SS/0143**
IRAS project ID: **202404**

Thank you for your letter of 8 September 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Ms Joyce Clearie, joyce.clearie@nhslothian.scot.nhs.uk.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).
Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

NHS
Lothian

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Clinical Trials Cover 2016/2017]		
GP/consultant information sheets or letters [Phase 2]		08 September 2016
GP/consultant information sheets or letters [Phase 3]		08 September 2016
Interview schedules or topic guides for participants [Phase 2 Discussion Schedule]		
IRAS Application Form [IRAS_Form_03082016]		03 August 2016
Letter from funder		13 July 2016
Letters of invitation to participant [Phase 1]	1	08 August 2016
Letters of invitation to participant [Phase 2]	1	08 August 2016
Letters of invitation to participant [Phase 3]	1	08 August 2016
Other [Public and Employers Liability 2016/2017]		01 August 2016
Other [Protocol]	1.3	08 August 2016
Other [Questionnaire Booklet]		08 September 2016
Participant consent form [Phase 1]	1	30 August 2016
Participant consent form [Phase 2]	1	30 August 2016
Participant consent form [Phase 3]	1	30 August 2016
Participant information sheet (PIS) [Phase 1]	1	30 August 2016
Participant information sheet (PIS) [Phase 2]	1	30 August 2016
Participant information sheet (PIS) [Phase 3]	1	30 August 2016
Sample diary card/patient card [Phase 3 Sample Exercise Manual]		
Sample diary card/patient card [Phase 3 Sample Exercise Diary]		
Summary CV for Chief Investigator (CI) [CI Summary CV]		
Summary CV for student [Student CV]		13 July 2016
Summary CV for supervisor (student research) [Supervisor CV]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Patient Flowchart]		
Validated questionnaire [Phase 1 Stage of Change Questionnaire]		
Validated questionnaire [Phase 1 Physical Activity Questionnaire]		
Validated questionnaire [Phase 1 & 3 Fatigue Questionnaire]		
Validated questionnaire [Phase 3 Prostate Cancer Specific Questionnaire]		
Validated questionnaire [Phase 3 General Health Questionnaire]		
Cover letter re PO		8 September 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review
Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback
The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training
We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

16/SS/0143	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Ms Joanne Mair
Chair

Email:joyce.clearie@nhslothian.scot.nhs.uk

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: *Mrs Samantha King*
Susan Ridge, Newcastle Joint Research Office

Appendix 1c. *Local Research and Development Approval*

From: White, Michael
Sent: 12 October 2016 15:13
To: Aning, Jonathan
Cc: Rix, David; 'John Saxton (john.saxton@northumbria.ac.uk)'; 'samantha.king@northumbria.ac.uk'; Robson, Wendy (Urology); 'Langhorne Lynnd (THE NEWCASTLE UPON TYNE HOSPITALS NHS FOUNDATION TRUST) (lynnd.langhorne@nhs.net)'; Finance Research and Development Team
Subject: 7832 Confirmation of Capacity and Capability

Dear Dr Aning,

Confirmation of Capacity and Capability at The Newcastle upon Tyne Hospitals NHS Foundation Trust

R&D: 7832
IRAS: 202404
Full Study Title: Supported progressive resistance exercise for countering the adverse side effects of prostate cancer treatment
Number of Patients: 140

This email confirms that **The Newcastle upon Tyne Hospitals NHS Foundation Trust** has the capacity and capability to deliver the above referenced study. Please find attached the signed contract as confirmation.

The NIHR requires NHS organisations to recruit patients to CLRN Portfolio studies within 30 days from the date of last contract signature. The 30 day deadline for recruiting the first patient is therefore 10th November 2016.

Please note: the Department of Health 70 day bench mark requires recruitment for clinical trials within 70 days of site selection. The 70 day deadline for recruiting the first patient is therefore 1st November 2016.

If you wish to discuss further, please do not hesitate to contact me.

Kind regards
Michael

Michael White
R&D Officer
Joint Research Office, Level 1, Regent Point
Regent Farm Road, Gosforth
Newcastle upon Tyne, NE3 3HD
http://www.newcastlejro.org.uk/

Appendix 2a. *Systematic Review Search Strategy*

Database	Search Strategy
MEDLINE	1. ((strength$ or resist$ or weight$) adj3 training).tw. 2. (progressive resist$).tw. 3. or/1-2 4. Exercise/ 5. Exercise Therapy/ 6. exercise$.tw. 7. or/4-6 8. (Resist$ training or strength$).tw. 9. and/7-8 10. or/3,9 11. randomized controlled trial.pt 12. controlled clinical trial.pt. 13. Randomized Controlled Trials/ 14. Random Allocation/ 15. Double Blind Method/ 16. Single Blind Method/ 17. or/11-16 18. Animals/ not Humans/ 19. 17 not 18 20. and/10,19
The Cochrane Library (Wiley)	#1 ((strength* or resist* or weight*) NEAR/3 training):ti,ab,kw #2 (progressive resist*):ti,ab,kw #3 #1 OR #2 #4 MeSH descriptor Exercise, this term only #5 MeSH descriptor Exercise Therapy, this term only #6 (exercise*):ti,ab,kw #7 (#4 OR #5 OR #6) #8 (resist* or strength*):ti,ab,kw #9 (#7 AND #8) # 10 (#3 OR #9)

Appendix 2b. *Trials Characteristics Included in the Systematic Review*

Author & year	Country	Population	Duration & frequency	Intervention Group	Control Group	Timing of outcomes	Funding & conflicts of interest
Ades et al. 1996	USA	RT = 69.9 ± 4 yrs CON = 70.7 ± 5 yrs Male and female Healthy elderly	12 weeks 3 d per week	Supervision not reported Free weights and weight machines 3 sets of 8 reps at 50% 1RM with progression to 80% by week 9	Continued with habitual activities	Baseline and 12 weeks	Grants from National Institute of Health and General Clinical Research Centres.
Afshar et al. 2010	Iran	RT = 51 ± 16.4 yrs AT = 50.7 ± 21.1 yrs CON = 53 ± 19.4 yrs Males Haemodialysis	8 weeks	Supervised by a physician Ankle weights 2 sets of 8 reps progressed to 3 sets	Not reported	Baseline and 8 weeks	Not reported
Ahmadizad et al. 2007	Iran	RT = 40.9 ± 3.2 yrs AT = 41.3 ± 5.1 yrs CON = 38.6 ± 3.2 yrs Male Sedentary obese	12 weeks 3 d per week	Supervision not reported Circuit resistance training 4 sets of 12 maximal reps at 11 stations 50–60% of 1RM in each station	Not reported	Baseline and 12 weeks	Tarbiat Moallem University of Sabzevar in Iran.
Ahmadizad et al. 2014	Iran	Total cohort 23.4 ± 0.6 yrs Male Sedentary overweight	8 weeks 3 d per week	Supervised Free weights, weight machines and body weight 1-2 weeks: 1 set of 10 reps 3-8 weeks: 2–3 sets of 20–30 reps NP: constant moderate intensity DUP: rotated loading LP: volume was decreased and the training intensity was increased each week	Not reported	Baseline and 8 weeks	Not reported
Almenning et al. 2015	Norway	Total cohort 27.2 ± 5.5 yrs Females	10 weeks 3 d per week	Supervised by an exercise physiologist at least 1 session a week 3 sets of 10 reps at 75% 1RM	Not reported	Baseline and 10 weeks	The Norwegian Fund for Research in Sports Medicine.

		Polycystic ovary syndrome					
Anderson et al. 2004	USA	RT = 26.4 ± 7.5 yrs AT = 20.9 ± 2.4 yrs CON = 26.6 ± 6.5 yrs Males Healthy sedentary	6 weeks 3 d per week	Supervision not reported Free-weight and machine exercises 2 sets of 10-15 reps	Refrain from systematic physical activity	Baseline and 6 weeks	Not reported
Andersen et al. 2008	Denmark	RT = 44 ± 9 yrs Fitness Training = 45 ± 9 yrs CON = 42 ± 8 yrs Females Trapezius myalgia	10 weeks 3 d per week	Supervised Free-weight and machine exercises 3 sets Intensity progressively increased from 12RM to 8RM	Health advice	Baseline and 10 weeks	Grants from Danish Medical Research Council and the Danish Rheumatism Association.
Andersen et al. 2014	Denmark	Total cohort = 68.2 ± 3.2 yrs Males Healthy elderly	16 weeks 2 d per week	Supervised Free-weight and machine exercises 0-4 weeks: 3 sets of 16-20 reps 5-8 weeks: 3 sets of 12 reps 9-12 weeks: 3 sets of 10 reps 13–16 weeks: 4 sets of 8 reps	Not reported	Baseline and 16 weeks	Supported by the FIFA Medical Assessment and Research Centre, The Danish Ministry of Culture, and Nordea-fonden, Denmark.
Andersen et al. 2016	USA	Total cohort = 68.1 ± 2.1 yrs Healthy elderly	36 weeks 2 d per week	Supervised Free weight, weight machines and body weight 0-4 weeks: 3 sets of 16–20RM 5-8 weeks: 3 sets of 12RM 9-12 week: 3 sets of 10RM 13-52 weeks: 4 sets of 8RM	Continued with habitual activities	Baseline and 36 weeks	Supported by the FIFA-Medical Assessment and Research Centre (Project 31964). The Danish Ministry of Culture (Kulturministeriets Udvalg for Idrætsforskning) (TKIF 2010-027), and Nordea-fonden (02-2011-4360).
Arora et al. 2009	India	RT = 49.6 ± 5.2 yrs AT= 52.2 ± 9.3 yrs CON = 58.4 ± 1.8 yrs Male and female Type 2 diabetes	8 weeks 2 d per week	Supervised 3 sets of 10 reps at 60-100% 1RM	Continued with habitual activities	Baseline and 8 weeks	Grant from University Grants Commission, Delhi, India.
Asad et al. 2012	Iran	RT = 21 ± 1.6 yrs AT = 22 ± 0.9 yrs Concurrent = 21.4 ± 2.1 yrs	8 weeks 3 d per week	Supervision not reported Free weights and weight machines 3 sets of 10-15 reps	Not reported	Baseline and 8 weeks	Not reported

		CON = 21.4 ± 1.1 yrs Male Healthy sedentary		Weeks 2-8: first set for 10-12 reps, 8-10 reps for second set and 4-8 reps for third set			
Augusto Libardi et al. 2012	Brazil	RT males = 47 ± 4.5 yrs RT females = 53.7 ± 3.7 yrs CON males = 49.5 ± 5.6 yrs CON females = 51.2 ± 6.4 yrs Males and females Healthy sedentary	16 weeks 3 d per week	Supervision not reported Free-weight, machine exercises and body weight 3 sets of 10 reps 9-16 weeks: 8 reps	Not reported	Baseline and 16 weeks	Supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico
Azarbayjani et al. 2014	Iran	RT = 23.1 ± 1.4 yrs AT = 23.3 ± 1.3 yrs Concurrent = 22.9 ± 1.7 yrs CON = 22.9 ± 1.7 yrs Males Healthy sedentary	12 weeks 3 d per week	Supervision not reported Free-weight and machine exercises 3 sets of 10 reps at 70% 1RM	Continued with habitual activities	Baseline and 12 weeks	Grant (90084702) from the Islamic Azad University, Central Tehran Branch grants commission.
Badrov et al. 2013	Canada	IHG3 = 23 ±4 yrs IHG5 = 27 ±6 yrs CON = 24 ± 8 yrs Females Healthy sedentary	8 weeks IHG3 - every other day IHG5 - five consecutive days	Supervision for 2 sessions a week Isometric hand grip at 30% MVC	Continued with habitual activities	Baseline, 4 and 8 weeks	Supported by the University of Windsor (810043; 809264; 808316; CLM), the Canadian Institutes of Health Research, Heart and Stroke/Richard Lewar Centre of Excellence Postdoctoral Fellowship, and an Ontario Graduate Scholarship.
Baldi & Snowling 2013	New Zealand	RT= 46.5 ± 2.1 yrs CON = 50.1 ± 1.3 yrs Females Type 2 diabetes	10 weeks 3 d per week	Supervised 1-2 circuits of 12 reps at 10RM (upper body) or 15RM (lower body)	Continued with habitual activities	Baseline and 10 weeks	Not reported
DeBarros et al. 2010	Brazil	RT = 31.8 ± 4.9 yrs CON = 32.4 ± 5.4 yrs	24-34 weeks 3 d per week	Supervised by the researcher for 1 session a week Elastic resistance band circuit	Continued with habitual activities	Baseline and 24 weeks	Supported by Coordenação de Aperfeiçoamento de Pessoal de

		Female Type 2 diabetes		Exercise intensity was controlled using a perceived exertion scale. Subjects advised to maintain an exercise intensity close to 5 or 6, which corresponds to a “somewhat heavy”.			Nível Superior with master’s fellowship grant.
Beck et al. 2013 *Beck et al. 2013*	USA	RT = 21.1 ± 2.5 yrs AT = 20.1 ± 1.1 yrs CON = 21.6 ± 2.9 yrs Normotensive CON = 21.6 ± 2.7 yrs Male and female young Pre-hypertensives *RT = 21.1 ± 0.6 yrs* *AT = 20.1 ± 0.9 yrs* *CON = 21.6 ± 0.8 yrs* *Normotensive CON = 21.6 ± 0.7 yrs* *Male and female* *Pre-hypertensives*	8 weeks 3 d per week	Supervision not reported Weight machines 2 sets of 8–12 reps to volitional fatigue *Weight machines* *2 sets of 8–12 reps to volitional fatigue*	Continued with habitual activities	Baseline and 8 weeks	Supported, in part, by a National Institutes of Health pre-doctoral training grant (NIH 5-T32-HL083810-04) awarded by the University of Florida Hypertension Centre. *Supported, in part, by a National Institutes of Health predoctoral training grant (NIH 5-T32-HL083810-04) awarded to D.T.B. by the University of Florida Hypertension Centre.*
Bell et al. 2000	Canada	Total cohort = 22.3 ± 3.3 yrs Male and female Physically active	12 weeks 3 d per week	Supervision not reported Free-weight and machine exercises 2-6 sets of 4-12 reps	Continued with habitual activities and asked to refrain from beginning any formal exercise training programme	Baseline, 6 and 12 weeks	Not reported
Beltran Valls et al. 2014	Italy	RT = 72 ± 1 yrs CON = 72 ± 1 yrs Male and female	12 weeks 2 d per week	Supervised Weight machines	Continued with habitual activities	Baseline and 12 weeks	Grants from the University of Rome “Foro Italico” (Research 2009) to D. C. The Lazio Regional

		Healthy elderly		1-2 weeks: 4 sets of 15 reps at 40–50 % 1RM 3-12 weeks: 3–4 sets of 10–12 reps at 70 % of baseline 1RM			Municipality (Agreement CRUL-Lazio n. 12650/2010) supported the post-doc scholarship to ID.
Boardley et al. 2007	USA	RT = 74.1 ± 6.2 yrs Combined = 75.3 ± 6 yrs AT = 73.2 ± 6.6 yrs CON = 75.9 ± 7.7 yrs Male and female Healthy elderly	16 weeks 3 d per week	Supervised by project staff for 2 sessions a week Elastic resistance bands 1-2 weeks: 1 set of 10 reps 3-16 weeks: 2 sets of 12 reps Theraband colour was changed so that it provided sufficient resistance to produce mild fatigue at the final rep	Not reported	Baseline, 8 and 16 weeks	Funded by the National Institute for Nursing Research grant #R01 NR04929. The Hygenic Corporation supplied the Thera-Band but had no other role in the study.
Borges & Carvalho 2014	Brazil	RT = 64.1 ± 12.5 yrs CON = 67.8 ± 9 yrs Male and female COPD	Completed a minimum of 3 sessions	Supervised Free weights and weight machines 2 sets of 9 reps Initial load was 80% 1RM and adjusted in subsequent sessions based on symptoms, Borg Dyspnea Scale scores, and patient fatigue	Normative daily care e.g. chest physiotherapy, non-invasive ventilation, and instructions to carry on with daily physical activities	Evaluated on the second day in hospital, at discharge, and 30 days post discharge	Not reported
Brentano et al. 2008	Brazil	Age not reported Female Post-menopausal	24 weeks 3 d per week	Supervision not reported Free-weight and machine exercises RT circuit: 2-3 sets of 10-20 reps at 45-60% 1RM RT: 2-4 sets of 6-20 reps at 45-80% 1RM	Continued with habitual activities	Baseline, 8, 16 and 24 weeks	Not reported
Brito et al. 2013	Brazil	Age not reported. Male and female HIV/AIDS	24 weeks. 3 d per week	Supervised Free-weight and machine exercises 3 sets of 8-10 reps at 80% 1RM	Continued with habitual activities and received	Baseline and 24 weeks	Not reported

					nutritional advice		
Broeder et al.1992	USA	Only report cohort 18-35 years Males Physically active	12 weeks 4 d per week	Supervised Free-weight and machine exercises 1-2 weeks: 10-12 reps 3-12 weeks: 10-12 reps on the first set, 8-10 reps on the second set, and 6-8 reps on the third set	Continued with habitual activities	Baseline and 12 weeks	Not reported
Brooks et al. 2007	USA	RT = 66 ± 2 yrs CON = 66 ± 1 yrs Males and females Type 2 diabetes	16 weeks 3 d per week	Supervision not reported Weight machines 3 sets of 8 reps 1-9 weeks: 60% 1RM 10-14 weeks: 70-80% 1RM	Continued with habitual activities and medications	Baseline and 16 weeks	Funded, in part, by the Brookdale Foundation, the USDA ARS agreement 58-1950-9-001, the NIH General Clinical Research Center M01 RR000054, and the International Life Sciences Institute North America.
Buchner et al. 1997	USA	RT = 74 yrs AT = 75 yrs AT + RT = 75 yrs CON = 75 yrs Male and female Healthy elderly	24-26 weeks 3 d per week	Supervised Weight machines 2 sets of 10 reps with the first set at 50-60% 1RM and the second set 75% 1RM	Continued with habitual activities	Baseline and 24 weeks Follow up at 28 weeks	Grants from the National Institute on Aging (UO1 AG09095), Centres for Disease Control and Prevention (R48 CCR002181), and the Department of Veterans Affairs.
Camargo et al. 2008	Brazil	RT = 29 ± 3 yrs AT = 29 ± 4 yrs CON = 30 ± 4 yrs Males Healthy sedentary	12 weeks 3 d per week	Supervised Weight machines 3 sets of 15 reps at 60% of 1RM	Continued with habitual activities	Baseline and 12 weeks	Partially supported by a grant from FIPE-Hospital de Clinicas de Porto Alegre and FAPICC.
Castaneda et al. 2002	USA	RT = 66 ± 2 yrs CON = 66 ± 1 yrs Male and female Type 2 diabetes	16 weeks 3 d per week	Supervision not reported 3 sets of 8 reps Weight machines 1-8 weeks: 60-80% of baseline 1RM 10-14 weeks: 70-80% of mid-study 1RM	Continued with medications and received a weekly phone call	Baseline and 16 weeks	Funded, in part, by Brookdale foundation in U.S. Department of Agriculture, the National Institutes of Health Clinical Research Centre and the International Life Sciences Institute, North America.
Christensen et al. 2014	Denmark	RT = 34.4 ± 7.6 yrs CON= 35.8 ± 8.9 yrs Male	9 weeks 3 d per week	Supervised 1-2 weeks: 3 sets of 15 reps at 15RM	Received standard care and continued	Baseline and 9 weeks	Supported by Copenhagen University Hospital, the Beckett Foundation and the Centre for

		Disseminated germ cell cancer		3-9 weeks: 4 sets of 10 reps at 10-12RM	with medications		Integrated Rehabilitation of Cancer Patients.
Colado et al. 2009	Spain	RT = 54 ± 2.8 yrs Aquatic = 54.7 ± 2 yrs CON = 52.9 ± 1.9 yrs Female Post-menopausal	24 weeks	Supervised Free-weight, machine and body weight exercises 1-12 weeks: 8 exercise circuit, 1 set of 20 reps with 30 sec active rest between sets, 1 set upper body, 2 sets lower body. 12-24 weeks: 10 exercise circuit, 1 set of 20 reps	Not reported	Baseline and 24 weeks	Funding (PMAFI-PI-01/1C/04) from the Research Funds Program of the Catholic University San Antonio in Murcia (Spain).
Conceição et al. 2013	Brazil	RT = 53.4 ± 4 yrs CON = 53 ± 5.7 yrs Females Post-menopausal	16 weeks 3 d per week	Supervision not reported Free-weight, machine and body weight exercises 1-8 weeks: 3 sets of 10 reps at 10RM with 60 s rest between sets 9-16 weeks: 3 sets of 8 reps at 8RM with 90 s rest between sets	Continued with habitual activities	Baseline and 16 weeks	Funding from the São Paulo Research Foundation (FAPESP) for financial support (2012/09709-0).
Courneya et al. 2007 *Courneya et al. 2010*	Canada	RT= 49.5 yrs AT = 49 yrs Control = 49 yrs Females Breast cancer	18 weeks *Not reported*	Supervised Weight machines 2 sets of 8-12 reps at 60% to 70% 1RM	Continued with habitual activity	Baseline, 9 (only for subjective measures) and 18 weeks	None reported G*rant from the Canadian Breast Cancer Research Alliance. Also supported by a Doctoral Research Award from the Canadian Institutes of Health Research, the Canada Research Chairs Program, a Research Team Grant from the National Cancer Institute of Canada with funds from the Canadian Cancer Society and the National Cancer Institute of Canada Canadian Cancer Society Socio-behavioural Cancer Research Network and a New Investigator Award from the Heart and Stroke Foundation of Canada.*
Croymans et al. 2013	USA	RT = 21.5 yrs Control = 22 yrs	12 weeks 3 d per week	Supervised	Completed no	Baseline and 12 weeks	Supported by the American Heart Association (BGIA no 0765139Y

		Male Sedentary obese		Free-weight, machine and body weight exercises 1-2 weeks: 2 sets of 12–15 reps at 100% of estimated 12–15RM 3–7 weeks: 3 sets of 8–12 reps, at 100% of 8–12RM 8–12: weeks: 6–8 reps at 6–8RM	resistance exercise for the duration of the intervention		to CKR), the National Heart, Lung and Blood Institute (P50 HL105188 to CKR) and the National Centre for Advancing Translational Sciences through UCLA CTSI Grant UL1TR000124 RAH and the American Heart Association (10SDG305006).
Davidson et al. 2009	USA	FEMALES: RT = 67.6 ± 4.2 yrs AT = 69.1 ± 6.5 yrs Combined = 66.5 ± 5.3 yrs CON = 66.7 ± 3.7 yrs MALES: RT = 67.4 ± 6 yrs AT = 68.8 ± 6 yrs Combined = 67.1 ± 5 yrs CON = 67.4 ± 3.8 yrs Male and female Sedentary obese	24 weeks 3 d per week	Supervision not reported Free-weight, machine and body weight exercises 1 set Each exercise was performed until volitional fatigue	Continued with habitual activities	Baseline and 24 weeks	Supported by research grant MT 13448 from the Canadian Institutes of Health Research.
DeLima et al. 2012	Brazil	RT linear periodization = 25.2 ± 4.4 yrs RT undulating periodization = 27.4 ± 2.8 yrs CON = 23.4 ± 1.3 yrs Female Healthy sedentary	12 weeks 3 d per week	Supervised Free-weight, machine and body weight exercises 3 sets until failure RT linear: 3 sets of 30RM, in the second week 3 sets of 25RM, in the third week 3 sets of 20RM and in the fourth week 3 sets of 15RM RT undulating: weeks 1, 3, 5, 7, 9 and 11, participants trained on days 1 and 2 with 3 sets of 30RM and on days 3 and 4 with 3 sets of 25RM. Weeks 2, 4, 6, 8, 10 and 12, participants	Continued with habitual activity	Baseline and 12 weeks	Not reported

				trained on days 1 and 2 with 3 sets of 20RM and on days 3 and 4 with 3 sets of 15RM.			
DeSouza et al. 2014	Brazil	RT = 25.9 ± 6.4 yrs Interval = 24 ± 7.5 yrs Concurrent = 22.5 ± 3.9 yrs CON = 22.1 ± 2.4 yrs Male Physically active	8 weeks 2 d per week	Supervision not reported 3-5 sets of 6-12RM	Not reported	Baseline and 8 weeks	Not reported
Deibert et al. 2011	Germany	RT = 55.5 ± 4.8 yrs RT + supplement = 55.9 ± 3.5 yrs CON = 55.8 ± 5.5 yrs Male Healthy sedentary	12 weeks 2 d per week	Supervised Weight machines 1–4 weeks: 25 reps 5–9 weeks: 15 reps 10-12 weeks: 10 reps	Continued with habitual activity and received lifestyle advice	Baseline and 12 weeks	Grants from Almased Wellness Corp.
DeVallance et al. 2016	USA	RT = 51 ± 3 yrs CON = 44 ± 3 yrs Male and female Metabolic syndrome	8 weeks 3 d per week	Supervision not reported Weight machines 3 sets of 8-12 reps 1–2 weeks: 60% of 1RM 3–4 weeks: 70% of 1RM 5–6 weeks: 80% of 1RM 7–8 weeks: 85% of 1RM	Continued with habitual activity	Baseline and 8 weeks	Supported in part by the American Heart Association Grant 11CRP7370056, National Heart, Lung, and Blood Institute Grant T32-HL-090610, and National Institute of General Medical Sciences of the National Institutes of Health under Award U54-GM-104942 and 1P20 GM109098, STEM Mountains of Excellence Fellowship.
Donges et al. 2010	Australia	Age not reported. Male and female Healthy sedentary	10 weeks 3 d per week	Supervised Weight machine exercises 10RM that is reported to approximate with 75% of a 1RM	Continued with habitual activity	Baseline and 10 weeks	Funded by Charles Sturt University.
Dunstan et al. 1998	Australia	RT Circuit = 50.3 ± 7.7 yrs CON = 51.1 ± 7.6 yrs Male and female	8 weeks 3 d per week	Supervised Free-weight, machine and body weight exercises 1-2 weeks: 2 sets of 10-15 reps at 50–55% 1RM	Continued with habitual activities	Baseline and 8 weeks	Supported by a National Health and Medical Research Council program grant ‘Studies in hypertension and vascular disease’.

		Type 2 diabetes		3-8 weeks: 3 sets of 10-15 reps at 50–55% 1RM			
Edge et al. 2006	Australia	Total cohort = 18 ± 1 yrs Female Physically active	5 weeks	Supervision not reported Free weights and machines 1-2 weeks: 2-3 sets of 15-20 reps 3-5 weeks: 3-5 sets of 15-20 reps Set 1 at 70% 3RM; set 2 at 60% 3RM; sets 3–5 at 50% 3RM	Not reported	Baseline and 5 weeks	Not reported
Egana et al. 2010	Ireland	RT = 69 ± 5 yrs CON = 64 ± 4 yrs Female Healthy elderly	12 weeks 2 d per week	Supervised Therabands 2 sets at 100% 10RM	Continued with habitual activity	Baseline and 12 weeks	Not reported
Elliott et al. 2002	UK	RT = 58 ± 4 yrs CON = 53 ± 3 yrs Female Post-menopausal	8 weeks 3 d per week	Supervision not reported 3 sets of 8 reps at 80% 10RM	Continued with habitual activity	Baseline and 8 weeks Follow-up at 16 weeks	Not reported
Fahlman et al. 2002	USA	RT = 73 ± 3 yrs AT = 76 ± 5 yrs CON = 74 ± 5 yrs Female Healthy elderly	10 weeks 3 d per week	Supervision not reported Weight machines 3 sets of 8 reps at 8RM	Continued with habitual activity	Baseline and 10 weeks	Not reported
Fatouros et al. 2005	Greece	RT low intensity = 71.1 ± 3.6 yrs RT mod intensity = 69.7 ± 3.8 yrs RT high intensity = 70.8 ± 2.8 yrs CON = 69.8 ± 5.1 yrs Male Sedentary obese	24 weeks 3 d per week	Supervised Weight machines and body weight RT low intensity – 1-8 weeks: 2 sets, 9-24 weeks: 3 sets, 45-50% 1RM RT mod intensity – 1-8 weeks: 2 sets, 9-24 weeks: 3 sets, 60-65% 1RM RT high intensity – 1-8 weeks: 2 sets, 9-24 weeks: 3 sets, 80-85% 1RM	Not reported	Baseline and 24 weeks Follow up at 48 weeks	Not reported
Fenkci et al. 2006	Turkey	RT = 44 ± 10.2 yrs AT = 41.7 ± 6.9 yrs	12 weeks 3 d per week	Supervision not reported Weight machines	Continued with habitual activity	Baseline and 12 weeks	Not reported

		CON = 43.8 ± 7.4 yrs Female Sedentary obese		1 week: 1 set of 10 reps of 40-60% 1RM 2 weeks: 2 sets of 10 reps of 40-60% 1RM 3 weeks: 3 sets of 10 reps of 40-60% 1RM 4-12 weeks: 3 sets of 75-80% 1RM			
Figueroa et al. 2012 *Figueroa et al. 2013* *Figueroa et al. 2013*	USA	Not reported. *RT with WBV = 56 ± 3 yrs* *CON = 56 ± 3 yrs* *RT with WBV = 55.5 ± 0.7 yrs* *CON = 56.4 ± 1 yrs* Female Sedentary obese	6 weeks *12 weeks* 3 d per week	Supervised Whole body vibration with free weights Vibration intensity was progressed by increasing the frequency (25–30Hz) and amplitude (1–2mm). The duration of the sets and rest periods was progressively increased (30–60 s) and decreased (60–30 s), respectively.	Continued with habitual activity	Baseline and 6 weeks	Not reported
Franklin et al. 2015	USA	RT = 30.3 ± 5.4 yrs CON = 30.8 ± 9.0 yrs Female Sedentary obese	8 weeks 2 d per week	Supervised Free weights and machines 2-3 sets of 10 reps at 80–90% 10RM	Continued with habitual activity and offered educational material	Baseline and 8 weeks	Supported by the National Heart, Lung, and Blood Institute grants lK23HL85614, RO1HL095701, and HL095701-01A2S, and the University of Illinois at Chicago, Centre for Clinical and Translational Science, award UL1RR029879 from the National Centre for Research Resources.
Garcia-Lopez et al. 2007	Finland	RT = 54.9 ± 1.9 yrs AT = 53.6 ± 2.4 yrs CON = 53.3 ± 2.5 yrs Male Healthy sedentary	21 weeks 2 d per week	Supervised Weight machines 1-7 weeks: 2-4 sets of 8-15 reps at 40–70% 1RM 8–14 weeks: 2-5 sets of 5-12 reps at 60–80% 1RM 15-21 weeks:3-5 sets of 5-10 reps at 60–85% 1RM	Continued with habitual activity	Baseline, 10.5 (not control group) and 21 weeks	Funded, in part, by a grant from the Ministry of Education, Finland.
Gater et al. 1992	USA	Physically active	10 weeks	Not reported		Baseline and 10 weeks	Grant from Ross Laboratories, the Achievement Reward for College

							Scientists Foundation, and National Heart, Lung and Blood Institute Research Services Award HL-07249.
Gelecek et al. 2012	Turkey	RT = 54.3 ± 5.3 yrs CON = 51.8 ± 3.7 yrs Female Post-menopausal	12 weeks 3 d per week	Supervised Free weights and machines 2 sets of 8-12 reps at 60% 1RM	Continued with habitual activity	Baseline and 12 weeks	Funded by the Department of Scientific Research Projects of Dokuz Eylül University.
Gettman et al. 1978	USA	Physically active	20 weeks 3 d per week	Supervision not reported Free weight, weight machines and body weight 1-6 weeks: 10-20 reps per set at 50% 1RM 7-20 weeks: 15 reps per set at 50% 1RM		Baseline and 20 weeks	Supported by the International Association of Chiefs of Police/Law Enforcement Assistance Administration, Grant No. 76-NI-99-001
Gordon et al. 2006	UK	RT = 67 ± 2 yrs CON = 67 ± 2 yrs Male and female Type 2 diabetes	16 weeks 3 d per week	Supervision not reported Weight machines 3 sets of 8 reps at 60-65% 1RM	Continued with habitual activity and received weekly phone calls	Baseline and 16 weeks	Supported by the Brookdale Foundation, USDA ARS Cooperative Agreement 58-1950-9-00 I and NIH GCRC grant MOl RR000054.
Greenwood et al. 2015	USA	RT = 54.6 ± 10.6 yrs AT = 53.9 ± 10.7 yrs CON = 49.5 ± 10.6 yrs Male and female Kidney transplant recipients	12 weeks 3 d per week	Supervised Elastic resistance bands, ankle weights and free weights 1-2 sets of 10 reps at 80% 1RM	Usual care was followed and so seen routinely in the transplantation clinic	Baseline and 12 weeks	Funded by an NIHR Doctoral Research Fellowship. The study was hosted in the King's College Hospital NIHR clinical research facility. This article presents independent research funded by the NIHR.
Gregory et al. 2013	USA	Total cohort = 20.3 ± 0.3 yrs Female Physically active	8 weeks 3 d per week	Supervised Free-weight, machine and body weight exercises 3 sets of 3-12RM	Continued with habitual activity	Baseline, 4 and 8 weeks	Grant from the U.S. Army Medical Research and Materiel Command Bone Health and Military Medical Readiness Research Program to BCN.
Hagberg et al. 1989	USA	Total cohort = 72 ± 3 yrs Male and female Healthy sedentary	26 weeks 3 d per week	Supervised Weight machines 8-12 reps	Not reported	Baseline, 13 (not controls and 26 weeks	Funded, in part, by a grant from the Diabetes Treatment Centres of America Foundation.

Hagerman et al. 2000	UK	RT = 63.7 ± 5 yrs CON = 66.2 ± 6.5 yrs Male Healthy elderly	16 weeks 2 d per week	Supervision not reported Free-weight, machine and body weight exercises 1 set of 10 reps at 85-90% 1RM followed by 3 sets to failure of 6-8 reps at 85-90% 1RM	Not reported	Baseline and 16 weeks	Not reported
Hagstrom et al. 2016	Australia	RT - 51.2 ± 8.5 yrs CON - 52.7 ± 9.4 yrs Female Breast cancer	16 weeks 3 d per week	Supervised Free weight and weight machines 3 sets of 8-10 reps at 8RM		Baseline and 16 weeks	Supported by a grant from Western Sydney University, Australia.
Hallsworth et al. 2011 *Jakovljevic et al.*	Finland	RT = 52 ± 13.3 yrs CON = 62 ± 7.4 yrs *RT = 49 ± 13 yrs* *CON= 62 ± 7 yrs* Male and female Non-alcoholic fatty liver disease	8 weeks 3 d per week	Supervision biweekly Free weights and weight machine 2 sets at 50% 1RM	Not reported	Baseline and 8 weeks	Not reported
Hautala et al. 2006	Canada	RT = 42 ± 1 yrs CON = 41 ± 1 yrs Male and female Healthy sedentary	2 weeks 5 d per week	Supervised 1 set of 8-12 reps	Continued with habitual activity	Baseline and 2 weeks	Funding from the EU Seventh Framework Programme (FP7/2007-2013) under grant agreement no Health-F2-2009-241762, for the project FLIP; the MRC; the UK NIHR Biomedical Research Centre on Ageing and Age-Related Diseases and Diabetes UK.
Haykowsky et al. 2000	Canada	RT = 68 ± 3 yrs CON = 68 ± 4 yrs Male Healthy elderly	16 weeks 3 d per week	Supervision not reported Free weights and weight machine 3-10 reps at 60-80% 1RM	Continued with habitual activity	Baseline, 4, 8, 12 and 16 weeks	Grants from the Ministry of Education (Helsinki, Finland) and the Medical Council of the Academy of Finland (Helsinki, Finland).
Haykowsky et al. 2005	Iran	RT = 70 ± 4 yrs AT = 66 ± 3 yrs Combined = 68 ± 6 yrs CON = 67 ± 4 yrs Female Healthy elderly	12 weeks 3 d per week	Supervised 2 sets of 10 reps at 50% 1RM	Continued with habitual activity	Baseline and 12 weeks	Not reported

Hedayati et al. 2012	USA	RT 40% 1RM = 23.2 ± 1 yrs RT 80% 1RM = 21.9 ± 1.5 yrs CON = 20.8 ± 1 yrs Female Physically active	4 weeks 4 d per week	Supervision not reported Free weights and machines 3 sets of 8-11 reps	Not reported	Baseline and 4 weeks	Not reported
Heffernan et al. 2013	USA	RT = 60 ± 2 yrs CON = 63 ± 2 yrs Sex not reported. Pre-hypertensive and newly diagnosed/never-treated hypertensive	12 weeks 3 d per week	Supervised Weight machines 2 sets of 12-15 reps at 40% 1RM for upper body and 60% 1RM for lower body	Continued with habitual activity	Baseline and 12 weeks	Not reported
Hendrickson et al. 2010	USA	RT = 21 ± 0.5 yrs AT = 21 ± 0.4 yrs Combined = 20 ± 0.4 yrs CON = 20 ± 0.5 yrs Female Physically active	12 weeks 3 d per week	Supervised Free weights, machine and body weight exercises 3–6 weeks - ‘‘light’’ days at 12RM, ‘‘moderate’’ days at 8–10RM, and ‘‘heavy’’ days at 6–8RM loads. 8–11 weeks - ‘‘light’’ days at 12RM, ‘‘moderate’’ days at 6–8RM, and ‘‘heavy’’ days at 3–5RM	Continued with habitual activity	Baseline and 12 weeks	Not reported
Hiatt et al. 1994 *Hiatt et al. 1996*	Finland	RT = 67 ± 6 yrs AT = 67 ± 7 yrs CON = 67 ± 5 yrs Male Peripheral artery disease	12 weeks 4 d per week *3 d per week*	Supervised Cuff weight secured to the leg 3 sets or 6RM	Continued with habitual activity	Baseline and 12 weeks	Funded, in part, by a grant from the Medical Research and Material Command Bone Health Research Program to BCN.
Hoff et al. 2007	Norway	RT = 62.8 ± 1.4 yrs CON = 60.6 ± 3.0 yrs Male and female Chronic obstructive pulmonary disease	8 weeks 3 d per week	Supervision not reported 4 sets of 5 reps at 85-90% 1RM	Continued with habitual activity	Baseline and 8 weeks	Grant H133G90114 from the National Institute on Disability and Rehabilitation Research. Dr Hiatt is the recipient of a National Institutes of Health Academic Award in Vascular Disease.

Holviala et al. 2012	Belgium	RT = 56.5 ± 7.6 yrs AT = 55.5 ± 8.7 yrs Combined = 56.9 ± 7.5 yrs CON = 56.7 ± 7.5 yrs Male Healthy sedentary	21 weeks 2 d per week	Supervised Weight machines 1-7 weeks - 40–60% of 1RM 8-14 weeks - 60–80% of 1RM 15-21 weeks - 70–85% of the 1RM	Continued with habitual activity	Baseline and 21 weeks	Not reported
Hoof et al. 1996	Canada	Age not reported. Male Healthy sedentary	16 weeks 3 d per week	Supervised Weight machines 1-4 weeks – 3 sets of 12 reps at 70%1RM 5-16 weeks - 3 sets of 10 reps at 70% 1RM followed by 4 reps at 90% 1RM	Continued with habitual activity	Baseline and 16 weeks	Funded, in part, by the Norwegian Research Council by providing a Professor II position for Dr Richardson, grant HL-17731 from the National Heart, Lung, and Blood Institute and Tobacco Related Disease Research Program grant #15RT-0100.
Horne et al. 1996	Finland	Total cohort = 22.3 ± 3.3 yrs Male and female Physically active	12 weeks 3 d per week	Supervision not reported Machines and free weights	Not reported	Baseline, 6 and 12 weeks	Grants from the Belgian Ministry of Defence.
Hu et al. 2009	USA	RT = 32.2 ± 7.2 yrs CON = 31 ± 7.5 yrs Males Healthy sedentary	10 weeks 2-3 d per week	Supervised	Continued with habitual activity	Baseline and 10 weeks	Not reported
Huffman et al. 2014	Norway	Age not reported. Male and female Metabolic risk factors	24 weeks 3 d per week	Supervised Weight machines 3 sets of 8-12 reps	Not reported	Baseline and 24 weeks	Grants from the National Technology Agency of Finland, the Ministry of Education of Finland, Juho Vainio Foundation and partially funded by the National Science Foundation of Guangdong Province (815100760100004), China.
Husby et al. 2009 *Husby et al. 2010*	USA	RT = 58 ± 5 yrs CON = 56 ± 8 yrs Male and female Total hip arthroplasty	4 weeks post-operative 5 d per week	Supervised Weight machines 4 sets of 5 reps at 85% 1RM	Usual care involving conventional rehabilitation program following	Pre-operative, 1 week post-operative, 5 week Follow up at 24 and 52 weeks	Supported by the National Heart, Lung, and Blood Institute, National Institute on Aging and National Institute of Arthritis and Musculoskeletal and Skin Diseases.

					total hip arthroplasty		
Irving et al. 2015	Denmark	Young: RT = 25 ± 1 yrs AT = 25 ± 1 yrs CON = 26 ± 1 yrs Combined = 26 ± 1 yrs Old: RT = 70 ± 1 yrs AT = 70 ± 1 yrs CON = 71 ± 2 yrs Combined = 71 ± 2 yrs Male and female Healthy sedentary	8 weeks 4 d per week	Supervised 4 sets of 8–10 reps	Continued with habitual activity	Baseline and 8 weeks	Supported by National Institute of Health grant R01-AG09531, RO1-DK41973, National Centre for Advancing Translational Science grants UL1-RR024150 and KL2-RR024151, CTSA Grant Number UL1- TR000135 from the National Centre for Advancing Translational Sciences a component of the National Institutes of Health.
Jay et al. 2011	Finland	RT = 44 ± 8 yrs CON = 43 ± 10 yrs Male and female Healthy sedentary	8 weeks 3 d per week	Supervised Kettlebells	Not reported	Baseline and 8 weeks	Funded by The National Research Centre for the Working Environment.
Kaikkonen et al. 2000	Brazil	RT = 42.5 ± 7 yrs AT = 41.6 ± 6 yrs CON = 41.9 ± 7 yrs Male and female Healthy sedentary	12 weeks 3 d per week	No supervision provided Weight machines 3 circuits of 10 stations	Continued with habitual activity	Baseline and 12 weeks	Not reported
Kanegusuku et al. 2011	Finland	RT = 63 ± 1 yrs Power Training = 65 ± 1 yrs CON = 63 ± 1 yrs Male Healthy elderly	16 weeks 2 d per week	Supervision not reported Weight machines RT: 2 sets, 10 reps at 70% to 4 sets, 4-6 reps, 85-90% PT: 3 sets, 7 reps, 30% to 4 sets, 4-6 reps, 45-50%	Continued with habitual activity	Baseline and 16 weeks	Supported by FAPESP (#07/56653-1 and #07/00788-6), CNPq (#471600/2008-3), CAPES, and Head of the Psychopharmacology Incentive Fund Association.
Karavirta et al. 2009 *Karavirta et al. 2011*	Finland	RT = 56 ± 6 yrs AT = 54 ± 8 yrs Combined = 56 ± 7 yrs CON = 54 ± 8 yrs Male Healthy sedentary	21 weeks 2 d per week	Supervised Weight machines and body weight 1-7 weeks: 3 sets of 15-30 reps at 40–60% 1RM 8-14 weeks: 2-4 sets of 6-12 reps at 60–80% 1RM	Continued with habitual activity	Baseline, 10.5 and 21 weeks	Partially supported by grants from the Ministry of Education, Finland, Central Finland Health Care District, Jyväskylä, Finland, and Polar Electro Oy. *Partly supported by the Ministry of Education, Finland and the Juho Vainio Foundation, Finland.*

				15-21 weeks: 2-4 sets of 5-8 reps at 70–85% 1RM			
Karavirta et al. 2013	Japan	RT = 52 ± 8 yrs AT = 52 ± 7 yrs Combined = 49 ± 6 yrs CON = 52 ± 8 yrs Female Healthy sedentary	21 weeks 2 d per week	Supervised Weight machines and body weight 1-7 weeks: 3 sets of 12-20 reps at 40–60% 1RM 8-14 weeks: 2-4 sets of 5-12 reps at 60–80% 1RM 15-21 weeks: 2-4 sets of 5-8 reps at 70–85% 1RM	Not reported	Baseline, 10.5 and 21 weeks	Partly supported by the grants from the Ministry of Education and Culture, Central Finland Health Care District, Juho Vainio Foundation, Yrjo Jahnsson Foundation, the University of Jyväskylä, G. Harold and Leila Y. Mathers Charitable Foundation, James S. McDonnell Foundation, the National Institutes of Health-sponsored Research Resource for Complex Physiologic Signals, and the National Institute on Aging.
Karelis et al. 2015	Canada	RT - 45. 3± 14 yrs CON - 39.4 ± 8 yrs Male and female Kidney transplant patients	16 weeks 3 d per week	Supervised for 1 session a week Free weight, weight machines, body weight and elastic resistance 3 sets of 10 reps at 80% 1RM	Continued habitual activity	Baseline and 16 weeks	Supported by funds from investigator-sponsored research by AstellasPharma Canada, Inc (SG112). RRL is supported by the Fonds de Recherche du Québec - Santé and holds the J-A De Sève research chair. MJH is supported by the Canadian Institutes of Health Research and Canadian National Transplant Research Program and holds the Shire chair in nephrology and renal transplantation and regeneration at the Université de Montréal.
Kawano et al. 2006	Canada	RT = 20 ± 1 yrs Combined = 21 ± 1 yrs CON = 22 ± 1 yrs Male Healthy sedentary	20 weeks 3 d per week	Supervised Free weights, weight machines and body weight 3 sets at 50%1 RM	Continued with habitual activity	Baseline, 8 and 12 weeks Follow up at 24 and 32 weeks	Grants from the Ministry of Health, Labour and Welfare (H18-J-W-002), Japan Society for the Promotion of Science (17300226), and the National Institutes of Health in the US (AG20966).
Kell & Asmundson 2009	UK	RT = 40.1 ± 8.7 yrs AT = 36.7 ± 8.9 yrs CON = 35.3 ± 7.3 yrs	16 weeks 3 d per week	Supervised Free weights, weight machines and body weight	Continued with habitual activity	Baseline, 8 (not controls) and 16 weeks	Support from the Saskatchewan Health Research Foundation (New Investigator Grant) and the

		Male and female Chronic lumbar pain		4 sets of 10 reps at 53–72% 1RM			University of Alberta, Augustana Campus (travel grant).
Kemi et al. 2011	Iran	RT = 20.8 ± 2.4 yrs CON = 23 ± 2.9 yrs Female Healthy sedentary	8 weeks 3 d per week	Supervised Free weights 5 sets of 5 reps at 85% 1RM	Continued with habitual activity	Baseline and 8 weeks	Not reported
Kemmler et al. 2016	Germany	HIT = 42.9 ± 5.4 yrs CON = 42.5 ± 5.6 yrs Male Healthy sedentary	22 weeks 2-3 d per week	Supervised Weight machines Single set to failure of 6-8 reps	Continued with habitual activity	Baseline and 22 weeks	The authors are grateful for the support of the Staedtler-Stiftung (Nürnberg, Germany), Kieser Training (Erlangen, Germany), Post SV Nürnberg (Nürnberg, Germany), and Protein4you (Saarlouis, Germany).
Khorvash et al. 2012	USA	Total cohort = 25.1 ± 3.2 yrs Male Depression and anxiety	10 weeks 2 d per week	Supervision not reported Free weights, weight machines and body weight	Not reported	Baseline and 10 weeks	Not reported
Kim et al. 2011	Switzerland	Traditional RT = 20.8 ± 0.8 yrs Super slow RT = 19.5 ± 0.3 yrs CON = 21.5 ± 0.8 yrs Female Healthy sedentary	4 weeks	Supervision not reported Weight machines Traditional RT: 3 sets of 8 reps at 80% 1RM Super slow RT: 1 set to fatigue at 50% 1RM	Continued with habitual activity	Baseline and 4 weeks	Not reported
Ku et al. 2010	Korea	RT = 55.7 ± 6.2 yrs AT = 55.7 ± 7 yrs CON = 57.8 ± 8.1 yrs Female Type 2 diabetes	12 weeks 4 d per week	Supervised Elastic resistance bands 3 sets of 15-20 reps	Continued with habitual activity	Baseline and 12 weeks	Not reported
Kwon et al. 2010	Korea	RT = 55.7 ± 6.2 yrs CON = 57 ± 8 yrs Female Type 2 diabetes	12 weeks 3 d per week	Supervision not reported Elastic resistance bands 3 sets of 10-15 reps	Continued with habitual activity	Baseline and 12 weeks	Supported by Korean Diabetes Clinical Research Institution.
Kwon et al. 2011	Canada	RT = 56.3 ± 6.1 yrs AT = 55.5 ± 8.6 yrs	12 weeks 3 d per week	Supervision not reported Elastic resistance bands 3 sets of 10-15 reps	Continued with habitual activity	Baseline and 12 weeks	Not reported

		CON = 58.9 ± 5.7 yrs Female Type 2 diabetes					
Larose et al. 2010	USA	RT = 54.7 ± 7.5 yrs AT = 53.9 ± 6.6 yrs Combined = 53.5 ± 7.3 yrs CON = 54.8 ± 7.2 yrs Male and female Type 2 diabetes	Run in of 4 weeks followed by 22 weeks intervention. 2-3 d per week	Supervised Biweekly supervision after week 4 Weight machines 4 week run-in phase: 1-2 sets of 10 reps 5-22 weeks: 3 sets of 8 reps	Continue with habitual activity	Baseline and 22 weeks	Grants from the Canadian Institutes of Health Research (grant MCT-44155), Canadian Diabetes Association (The Lillian Hollefriend Grant), and the Interfaculty Grant program of the University of Ottawa.
LeMura et al. 2000	Australia	RT = 20 ± 1 yrs AT = 21 ± 2 yrs Cross training = 19 ± 2 yrs CON = 20 ± 1 yrs Female Healthy sedentary	16 weeks 3 d per week	Supervised Free weights, weight machines and body weight 1-2 weeks: 1 set of 8-10 reps at 60-70% 1RM 3-14 weeks: 3 sets of 8-10 reps at 60-70% 1RM	Continued with habitual activity and completed an activity log	Baseline, 8 and 16 weeks Follow up at 20 weeks	Not reported
Levinger et al. 2007 *Levinger et al. 2008* *Levinger et al. 2009*	Brazil	LoMFC = 48.5 ± 7.7 yrs LoMFT = 50.6 ± 5.1 yrs HiMFC = 52.3 ± 5.8 yrs HiMFT = 51.6 ± 7.1 yrs *LoMFC = 48.9 ± 7.4 yrs* *LoMFT = 50.3 ± 4.1 yrs* *HiMFC = 51.9 ± 5.8 yrs* *HiMFT = 51 ± 7 yrs* *LoMFC = 48.5 ± 7.7 yrs*	10 weeks 3 d per week	Supervised Weight machines Week 1: 2 sets of 15–20 reps at 40–50% 1RM Week 2: 3 sets of 15–20 reps at 50–60% 1RM 3-6 weeks: 3 sets of 12–15 reps at 60–75% 1RM 7-10 weeks: 3 sets 8 –12 reps at 75–85% 1RM	Continue with habitual activity	Baseline and 10 weeks	Not reported

		LoMFT = 50.6 ± 5.1 yrs *HiMFC = 52.3 ± 5.8 yrs* *HiMFT = 51.6 ± 7.1 yrs* Male and female Metabolic risk factors					
Libardi et al. 2011 *Libardi et al. 2012*	Taiwan	RT = 48.6 ± 5 yrs Concurrent = 48.5 ± 5.3 yrs CON = 49.1 ± 5.5 yrs Male Healthy sedentary *RT = 49.3 ± 4.8 yrs* *AT = 49.3 ± 5.4 yrs* *Concurrent = 48.5 ± 5.4 yrs* *CON = 49.1 ± 5.9 yrs* *Male* *Healthy sedentary*	16 weeks 3 d per week	Supervision not reported Free weights, weight machines and body weight 3 sets at 8-10RM	Not reported	Baseline and 16 weeks	Supported by the National Council of Technological and Scientific Development, Brazil. *Supported by the National Counsel of Technological and Scientific Development, Brazil.*
Lo et al. 2011	Australia	RT = 20.2 ± 1.4 yrs AT = 20 ± 0.7 yrs CON = 21.1 ± 1.7 yrs Male Healthy sedentary	24 weeks 3 d per week	Supervised Weight machines 1-8 weeks: 1 set at 15RM 9-16 weeks: 1 set of 10 reps at 75% 1RM 17-24 weeks: 2 sets of 4 reps at 90% 1RM	Not reported	Baseline and 24 weeks Follow- up at 48 weeks	Supported by the National Science Council, 95-2413-H-006-010, Taiwan, ROC.
Lovell et al. 2009 *Lovell et al. 2012*	USA	RT = 74.1 ± 2.7 yrs CON = 73.5 ± 3.3 yrs *RT = 74.1 ± 2.7 yrs* *AT = 75.2 ± 3.0 yrs*	16 weeks 3 d per week	Supervised Weight machine 3 sets of 6-10 reps at 50-90%1RM	Continued with habitual activity	Baseline, 4, 8, 12, and 16 weeks	Not reported

		CON = 73.5 ± 3.3 yrs Male Healthy elderly					
Madden et al. 2006	Iran	RT = 69.8 ± 1.5 yrs AT = 70 ± 2.6 yrs CON = 71.8 ± 1.2 yrs Female Healthy elderly	24 weeks 5 d per week	Supervised Free weights 3 sets of 8-12 reps at 85% 1RM	Continued with habitual activity	Baseline and 24 weeks	Supported by the AHA Washington Affiliate Grant-in-aid, the Medical research service of the department of veterans affairs
Mahdirejei et al. 2014	Australia	RT = 47.6 ± 7.7 yrs CON = 49.6 ± 8.1 yrs Male Type 2 diabetes	8 weeks 3 d per week	Supervised Free weights, weight machines and body weight 3 sets of 8-15 reps at 50-80% 1RM	Not reported	Baseline and 8 weeks	Supported by Islamic Azad University Sari Branch, Sari, Iran.
Maiorana et al. 1997	Australia	RT = 61.2 ± 8.4 yrs CON = 59 ± 8.7 yrs Male Coronary bypass graft	10 weeks	Supervised Free weights, weight machines and body weight 1-3 sets of 10-15 reps at 40-60% MVC	Continued with habitual activity	Baseline and 10 weeks	Not reported
Maiorana et al. 2011	USA	RT = 58.8 ± 3.5 yrs AT = 61.3 ± 2.8 yrs CON = 64.4 ± 2.4 yrs Male and female Stable chronic heart failure	12 weeks 3 d per week	Supervised Free weights, weight machines and body weight 1-6 weeks: 3 sets of 60 secs at 50-60% 1RM 7-12 weeks: 3 sets of 60 secs at 60-70% 1RM	Continued with habitual activity	Baseline, 6 and 12 weeks	Supported by the National Heart Foundation (Australia), the Dutch Heart Foundation (E. Dekker, stipend) and the Australian Research Council.
Malin et al. 2013	USA	Normal body fat = 21.9 ± 0.8 yrs High body fat = 21.0 ± 0.8 yrs CON = 20.9 ± 0.6 yrs Female Healthy sedentary	7 weeks 3 d per week	Supervised Free weights, weight machines and body weight 3 sets of 10-12 reps at 60% 1RM	Not reported	Baseline and 7 weeks	Funded by the Wayne State College Foundation.
Manning et al. 1991	USA	RT= 35.4 ± 2.6 yrs CON = 40.3 ± 5.5 yrs Female	12 weeks 3 d per week	Supervision not reported Free weights and weight machines	Not reported	Baseline, 4, 8 and 12 weeks	Supported, in part, by grant from the Valley Hospital and the William Paterson College of New Jersey.

		Sedentary obese		2-3 sets of 6-8 reps at 60-70% 1RM			
Marcinik et al. 1991	USA	RT= 29 ± 4 yrs CON = 30 ± 4 yrs Male Healthy sedentary	12 weeks 3 d per week	Supervised Free weights, weight machines and body weight 3 sets at 8-20RM	Continued with habitual activity	Baseline and 12 weeks	Not reported
Marcus et al. 2009	Portugal	RT Eccentric = 56.3 ± 6.4 yrs CON = 53.2 ± 6.5 yrs Females Impaired glucose tolerance	12 weeks 3 d per week	Supervised Weight machine	Continued with habitual activity	Baseline and 12 weeks	Supported by the Utah Building Interdisciplinary Research Careers in Women's Health Program (NIH grant 5K12HD043449-04).
Martins et al. 2010 *Martins et al. 2010*	USA	Total cohort = 76 ± 8 yrs Male and female Healthy sedentary *RT= 73.2 ± 6.5 yrs* *AT = 76.2 ± 7.4 yrs* *CON = 81.2 ± 7.9 yrs* *Males and females*	16 weeks 3 d per week	Supervised Elastic resistance bands 1-2 weeks: 1 set of 8 reps 3-4 weeks: 1 set of 12 reps 5-6 weeks: 2 sets of 8 reps 7-8 weeks: 2 sets of 10 reps 9-10 weeks: 2 sets of 12 reps 11-12 weeks: 2 sets of 15 reps 13-14 weeks: 3 sets of 12 reps 15-16 weeks: 3 sets of 15 reps	Not reported	Baseline and 16 weeks *Baseline and 16 weeks* *Follow-up at 32 weeks*	Supported by the Portuguese Foundation for Science and Technology and the Portuguese Institute of Sport.
McDermott et al. 2009	Australia	RT = 71.7 ± 8.7 yrs AT = 71.7 ± 8.7 yrs CON = 68.5 ± 11.9 yrs Male and female Peripheral artery disease	24 weeks 3 d per week	Supervised Weight machines 3 sets of 8 reps at 50-80% 1RM	Education sessions	Baseline and 24 weeks	Supported by grants R01-HL073551 from the National Heart, Lung, and Blood Institute and by RR-00048, National Institutes of Health and the Intramural Research Program, National Institutes on Aging.
McGuigan et al. 2001	USA	RT = 70 ± 6 yrs CON = 66 ± 6 yrs Male and female Peripheral artery disease	24 weeks 3 d per week	Supervised Free weights, weight machines and body weight 2 sets at 8-15RM	Continued with habitual activity	Baseline, 12 and 24 weeks	Supported by an American College of Sports Medicine Foundation Research Grant for doctoral students.
Mikesky et al. 1994	Canada	RT= 69.2 ± 4.0 yrs CON = 72.8 ± 5.7 yrs Male and female	12 weeks 3 d per week	Supervision for 1 session a week Body weight and elastic resistance bands	Attended two 3-h automobile driving	Baseline and 12 weeks	Grant from the Indiana University Grant-in-Aid program.

		Healthy elderly		1-2 weeks: 1 set of 12 reps 3-4 weeks: 2 sets of 12 reps 5-12 weeks: 2-3 sets of 12 reps	safety classes during weeks 4 and 8		
Millar et al. 2008	Japan	RT = 66 ± 1 yrs CON = 67 ± 2 yrs Male and female Healthy elderly	8 weeks 3 d per week	Supervision for 2 sessions a week Weight machine 1 set of 4 reps at 30-40% MVC	Not reported	Weekly for 8 weeks	Supported by an Ontario Graduate Scholarship award and a Natural Sciences and Engineering Research Council of Canada Discovery grant.
Miura et al. 2008	Japan	RT 1d·week = 69 ± 6.5 yrs RT 2d·week = 69.5 ± 7 yrs CON = 68.9 ± 7.5 yrs Female Healthy elderly	12 weeks 1 or 2 d per week	Supervised Free weights and elastic resistance bands 3–5 sets of 15–20 reps	Continued with habitual activity	Baseline and 12 weeks	Supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (15700441).
Miyachi et al. 2004	Norway	RT = 22 ± 1 yrs CON = 22 ± 1 yrs Male Healthy sedentary	16 weeks 3 d per week	Supervised Free weights, weight machines and body weight 3 sets of 12 reps at 80% 1RM	Continued with habitual activity	Baseline and 16 weeks Follow-up at 24 weeks	Grants from the National Institutes of Health (AG-020966), Japan Society for Promotion of Science (13780041 and 14208005) and the Meiji Yasuda Life Foundation.
Mosti et al. 2013	Norway	RT = 61.9 ± 5 yrs CON = 66.7 ± 7.4 yrs Females Osteoporosis or osteopenia	12 weeks 3 d per week	Supervised Weight machines 4 sets of 3–5 reps at 85–90% 1RM	Encouraged to follow current exercise guidelines for osteoporotic patients	Baseline and 12 weeks	Funded by the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology.
Mosti et al. 2014	Brazil	RT= 22.7 ± 2.2 yrs CON = 21.5 ± 2.2 yrs Female Healthy sedentary	12 weeks 3 d per week	Supervised Weight machines 4 sets of 3–5 reps at 85–90% 1RM	Encouraged to follow exercise advise in accordance with existing recommendations	Baseline and 12 weeks	Corresponding author funded by a PhD grant from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology.

Mota et al. 2013	Iran	RT = 67.5 ± 7 yrs CON = 66.8 ± 5.4 yrs Female Hypertensive	16 weeks 3 d per week	Supervised Free weights and weight machines 1-4 weeks: 3 sets of 10 reps 5-8 weeks: 3 sets of 12 reps at 60% 1RM 9-12 weeks: 3 sets of 10 reps at 70% 1RM 13-16 weeks: 3 sets of8 reps at 80% 1RM	Not reported	Baseline, 4, 8, 12 and 16 weeks	Not reported
Nikseresht et al. 2014 *Nikseresht et al. 2014*	Denmark	RT non-linear = 40.4 ± 5.2 yrs AT = 39.6 ± 3.7 yrs CON = 38.9 ± 4.1 yrs *RT non-linear = 40.4 ± 5.2 yrs* *AT = 39.6 ± 3.7 yrs* *Lean = 39 ± 5.9 yrs* *CON = 38.9 ± 4.1 yrs* Male Sedentary obese	12 weeks *12 weeks training. 4 weeks detraining period* *3 d per week*	Supervised Free weights and weight machines 1-4 sets of 2-20 reps at 40-95% 1RM	Continued with habitual activity	Baseline and 12 weeks *Baseline, 12 weeks and follow-up*	None reported. *Grants from the Ilam University of Medical Sciences, Ilam, Iran.*
Nybo et al. 2010	Japan	RT = 36 ± 2 yrs Interval running = 37 ± 3 yrs Prolonged running = 31 ± 2 yrs CON = 30 ± 2 yrs Male Healthy sedentary	12 weeks 3 d per week	Supervision not reported Free weights and weight machines 1-4 weeks: 4 sets of 12-16RM 5-12 weeks: 4 sets at 6-10RM	Continued with habitual activity	Baseline and 12 weeks	Supported by the Danish Ministry of Culture (Kulturministeriets Udvalg for Idrætsforskning).
O'Connor et al. 2017	UK	RT - 54.6 ± 10.6 yrs CON - 49.5 ± 10.6 yrs Male Kidney transplant recipients	12 weeks 3 d per week	Supervision for 2 sessions a week Free weights, weight machines and body weight 1-3 sets of 10 reps at 80% 1RM	Usual care were not provided with specific exercise guidance,	Baseline and 12 weeks	Funded by the NIHR. The study was hosted in the KCH NIHR Clinical Research Facility. This paper presents independent research funded by the NIHR.

					they received general exercise encouragement at routine appointments.		
Okamoto et al. 2006	Japan	RT Eccentric = 18.9 ± 0.3 yrs RT Concentric 19.1 ± 0.3 yrs CON = 19.9 ± 1.2 yrs Female Healthy sedentary	8 weeks 3 d per week	Supervised Free weights 5 sets of 8-10 reps 80-100% 1RM	Sedentary	Baseline and 8 weeks Follow-up (unclear duration)	Not reported
Okamoto et al. 2009a	Japan	RT Eccentric = 19.6 ± 0.4 yrs RT Concentric = 19.2 ± 0.3 yrs CON = 19.7 ± 0.3 yrs Male Physically active	10 weeks 2 d per week	Supervision not reported Free weights, weight machines and body weight 5 sets of 8-10 reps at 80% 1RM	Sedentary	Baseline and 10 weeks	Partially supported by the Ministry of Education, Science, Sports and Culture, Grant-in-Aid for Young Scientists (B), 19700539, 2007.
Okamoto et al. 2009b	Japan	RT Upper = 20.2 ± 0.4 yrs RT Lower = 20 ± 0.5 yrs CON = 20.1 ± 0.3 yrs Male and female Healthy sedentary	10 weeks 2 d per week	Supervised Free weights and weight machines 5 sets of 8-10 reps at 80% 1RM	Sedentary	Baseline and 10 weeks	Not reported
Okamoto et al. 2011	Japan	RT = 18.5 ± 0.5 yrs CON = 18.6 ± 0.5 yrs Male Healthy sedentary	10 weeks 2 d per week	Supervision not reported Free weights, weight machines and body weight 5 sets of 10 reps	Continued with habitual activity	Baseline and 10 weeks	Supported by the Grant-in-Aid for Scientists Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (21700680).

Okamoto et al. 2013	Norway	High then low intensity RT = 19.1 ± 0.7 yrs Low then high intensity RT = 19.3 ± 0.7 yrs CON = 19.1 ± 0.6 yrs Male and female Healthy sedentary	10 weeks 2 d per week	Supervision not reported Free weights and weight machines 3 sets of 10 reps to concentric failure	Sedentary	Baseline and 10 weeks	Not reported
Oldervoll et al. 2001	Brazil	RT = 42.2 ± 6 yrs AT = 42.6 ± 6 yrs CON = 43.9 ± 8.8 yrs Female Musculoskeletal pain	15 weeks 2 d per week	Supervision not reported 2-3 sets of 12-15 reps	Continued with habitual activity	Baseline and 15 weeks	Grant no. 111222/330 from the Norwegian Research Council and the University Hospital of Trondheim provided financial support for the employment of one of the instructors.
Oliveira et al. 2013	USA	RT = 22 ± 3 yrs CON = 23 ± 4 yrs Male Physically active	8 weeks 3 d per week	Supervised Isokinetic eccentric resistance exercise on weight machines 1-2 weeks: 2 sets of 8 reps 3-4 weeks: 4 sets of 8 reps 5-6 weeks: 6 sets of 8 reps 7-8 weeks: 3 sets of 8 reps	Continued with habitual activity	Baseline and 8 weeks	Supported by FAPESP and CNPq.
Olson 2006	Norway	RT = 38 ± 1 yrs CON = 38 ± 2 yrs Female Sedentary overweight	52 weeks 2 d per week	Supervised for the initial 16 weeks Free weights and weight machines 3 sets of 8–10 reps	Continued with habitual activity and provided with education material	Baseline and 52 weeks	Supported, in part, by the National Institutes of Health grant #:5R01DK060743-03, American Heart Association grant #:0410034Z and General Clinical Research Centre Program, NCRR/NIH #:M01-RR00400.
Panton et al. 1990	South Africa	RT = 72.2 ± 2.5 yrs Walk/jog = 71.8 ± 1.9 yrs CON = 72.1 ± 3 yrs Male and female Healthy sedentary	26 weeks 3 d per week	Supervised Weight machines 1 set of 8-12 reps	Continued with habitual activity	Baseline and 26 weeks	Not reported
Parr et al. 2009	Spain	RT Upper = 66 ± 13 yrs	6 weeks 3 d per week	Supervised	Continued with habitual	Baseline and 6 weeks	Not reported

		Conventional Exercise Rehab = 57 ± 14 yrs CON = 62 ± 10 yrs Male and female Peripheral artery disease		Free weights and weight machines 15-30 reps	activity and advised to walk at home		
Perez-Gomez et al. 2013	Canada	RT = 22 ± 1.2 yrs ET = 21.8 ± 1 yrs CON = 23.3 ± 2.5 yrs Male Physically active	10 weeks	Supervised Free weights and weight machines 50-90% of 1RM	Not reported	Baseline and 10 weeks	Not reported
Plotnikoff et al. 2010	USA	RT = 55 ± 12 yrs CON = 54 ± 12 yrs Male and female Type 2 diabetes	16 weeks 3 d per week	Supervision tapered Free weights and weight machines Week 1: 2 sets of 10–12 reps at 50–60% 1RM Week 2: 3 sets of 10-12 reps at 50-60% 1RM 3-8 weeks: 3 sets of 10-12 reps, intensity progressively increase to 70-80% 1RM Week 9: 2 sets of 10–12 reps at 70% 1RM 10-15 weeks: 3 sets of 8–10 reps at 70–85% 1RM Week 16: 2 sets of 8–10 reps at 80% 1RM.	Continued with habitual activity	Baseline and 16 weeks	Funded by the Canadian Institutes of Health Research, Strategic Initiative in Excellence, Innovation and Advancement for the Study of Obesity and Healthy Body Weight.
Poehlman et al. 2000	USA	RT = 28 ± 3 yrs AT = 29 ± 5 yrs CON = 28 ± 4 yrs Female Healthy sedentary	24 weeks 3 d per week	Supervised Free weights, weight machines and body weight 3 sets of 10 reps	Not reported	Baseline and 6 week	Grant from the Department of Defence (DE-950226), a post-doctoral fellowship from the American Heart Association, Maine/New Hampshire/Vermont affiliate, a grant from the Medical Research Council of Canada, and General Clinical Research Centre Grant RR-109.

Poehlman et al. 2002	USA	RT = 28 ± 3 yrs AT = 28 ± 4 yrs CON = 28 ± 4 yrs Female Healthy sedentary	24 weeks 3 d per week	Supervised Free weights, weight machines and body weight 3 sets of 10 reps	Not reported	Baseline and 6 weeks	Not reported
Pollock et al. 1991	USA	RT = 72.2 ± 2.5 yrs Walk/Jog = 71.8 ± 1.9 yrs CON = 72.1 ± 3 yrs Male and female Healthy elderly	26 weeks 3 d per week	Supervision not reported Weight machines 1 set of 10-12 reps	Not reported	Baseline and 26 weeks	Not reported
Prabhakaran et al. 1999	USA	RT = 28 ± 6 yrs CON = 26 ± 6 yrs Female Healthy sedentary	14 weeks 3 d per week	Supervised Free weights and weight machines 85% 1RM	Continued with habitual activity	Baseline and 24 weeks	Funded by the Yamanaka Fund.
Rana et al. 2008	USA	RT = 20.6 ± 1.9 yrs RT Low Velocity = 19.4 ± 1.3 yrs AT = 22.3 ± 3.9 yrs CON = 22.9 ± 2.4 yrs Female Healthy sedentary	6 weeks week 1 - 2 sessions weeks 2-6 - 3 days a week	Supervised Weight machines 3 sets at 6-10RM	Not reported	Baseline and 6 weeks	Not reported
Roberts et al. 2013	Sweden	Only report 18-35 yrs Male Sedentary obese	12 weeks 3 d per week	Supervised Free weights, weight machines and body weight 1–2 weeks: 2 sets of 12–15 reps 100% 12-15RM 3–7 weeks: 3 sets of 8–12 reps at 100% 8–12RM 8–12 weeks: 6–8 reps at 100% 6–8RM	Continued habitual activity	Baseline and 12 weeks	Supported by the American Heart Association (BGIA # 0765139Y), the National Heart, Lung and Blood Institute (P50 HL105188), the National Institute of Diabetes and Digestive and Kidney Diseases (DK090406) and the National Centre for Advancing Translational Sciences through UCLA CTSI Grant UL1TR000124.
Rodriguez-Miguelez et al. 2014	Spain	RT = 69.1 ± 1.1 yrs CON = 70 ± 0.9 yrs Male and female Healthy elderly	8 weeks 2 d per week	Supervision not reported Weight machines Week 1: 3 sets of 8 reps at 60% 1RM Week 2: 3 sets of 10 reps at 60% 1RM	Continued with habitual activity	Baseline and 10 weeks	Supported by Plan Nacional I+D+I DEP2010-17574, Spain.

				Week 3: 3 sets of 12 reps at 60% 1RM Week 4: 3 sets of 8 reps at 70% 1RM Week 5: 3 sets of 10 reps at 70% 1RM Week 6: 3 sets of 12 reps at 70% 1RM Week 7: 3 sets of 8 reps at 80% 1RM Week 8: 3 sets of 10 reps at 80% 1RM			
Romero-Areanas et al. 2007	Finland	High RT Circuit = 62.1 ± 6.3 yrs Traditional RT = 64.8 ± 4.5 yrs CON = 58 ± 5 yrs Male and female Healthy elderly	12 weeks 2 d per week	Supervised Weight machines High RT Circuit: 1-3 sets Traditional RT: 3 sets of 6-12 reps at 50-100% 6RM	Not reported	Baseline and 12 weeks	Grant 07/UPR20/10 from the Consejo Superior de Deportes.
Sallinen et al. 2007	USA	RT = 57.9 ± 6.6 yrs CON = 58.2 ± 6.1 yrs Male Healthy elderly	21 weeks 1-3 d per week	Supervised Free weights, weight machines and body weight 3-6 sets of 5-10 reps at 40-80% 1RM	Continued with habitual activity	Baseline, 21 and 42 weeks	Not reported
Sawyer et al. 2014	Germany	Total cohort = 20.6 ± 2 yrs Male Physically active	8 weeks 3 d per week	Supervision not reported Free weights, weight machines and body weight 3 sets at 8RM	Not reported	Baseline and 8 weeks	Not reported
Schiffer et al. 2011	Denmark	Total cohort = 22.6 ± 1.6 yrs Sex not reported Physically active	12 weeks 3 d per week	Supervised Weight machines 3 sets of 8-10 reps at 70-80% 1RM	Not reported	Baseline and 12 weeks	Supported by the World Anti-Doping Agency.
Schmidt et al. 2014	USA	RT = 69.1 ± 3.1 yrs Football = 68 ± 4 yrs CON = 67.4 ± 2.7 yrs Male Healthy elderly	52 weeks 2 d per week	Supervised Free weights, weight machines and body weight 1-4 weeks: 4 sets of 16-20RM 5-8 weeks: 4 sets of 12RM 9-12 weeks: 4 sets of 10RM 13-52 weeks: 4 sets of 8RM	Continued with habitual activity	Baseline, 12 and 52 weeks	Supported by Nordea-fonden, FIFA Medical Assessment and Research Centre, Preben and Anna Simondsen fonden, and The Danish Ministry of Culture.

Schmitz et al. 2002	USA	RT =41 ± 6 yrs CON = 42 ± 6 yrs Female Healthy sedentary	15 weeks 2 d per week	Supervised Free weights and weight machines 3 sets of 8-10 reps	Continued with habitual activity	Baseline and 15 weeks Follow up at 39 weeks	Supported by a Minnesota Obesity Centre Pilot and Feasibility Grant, NIH Grant DK50456 from the National Institute of Diabetes and Digestive and Kidney Diseases, University of Minnesota General Clinical Research Centre Grant M01-R00400, Tickle Family Fund for Breast Cancer Research, and Public Health Service Cancer Centre Support Grant P30 CA77398.
Schmitz et al. 2005	Canada	RT = 53.3 ± 8.7 yrs CON = 52.8 ± 7.6 yrs Female Breast cancer	26 weeks 2 d per week	Supervised for initial 13 weeks Free weights and weight machines 3 sets	Usual care of attending clinic appointments and taking medications and continued with habitual activity	Baseline, 24 and 52 weeks	S.G. Komen Foundation grant BCTR0100442 and NIH grants M01-RR00400 and T32 CA09607-15.
Segal et al. 2009	Iran	RT = 66.4 ± 7.6 yrs AT = 66.2 ± 6.8 yrs CON = 66.3 ± 7 yrs Male Prostate cancer	24 weeks 3 d per week	Supervised Free weights and weight machines 2 sets of 8-12 reps at 60-70% 1RM	Usual care of attending clinic appointments and taking medications and continued with habitual activity	Baseline and 24 weeks	Grant 013232 from the Canadian Prostate Cancer Research Fund.
Shamsoddini et al. 2015	South Africa	RT = 45.9 ± 7.3 yrs AT = 39.7 ± 6.3 yrs CON = 45.8 ± 7.3 yrs Males	8 weeks 3 d per week	Supervised Free weights, weight machines and body weight 1-2 weeks: 2 sets of 10 reps at 50% 1RM	Continued with habitual activity	Baseline and 8 weeks	Supported by Exercise Physiology Research Centre and Research Centre for Gastroenterology and Liver Disease in Baqiyatallah University of Medical Sciences, Tehran, IR Iran.

		Non-alcoholic fatty liver disease		3-4 weeks: 2 sets of 10 reps at 60% 1RM 5-6 weeks: 3 sets of 10 reps at 60% 1RM 7-8 weeks: 3 sets of 10 reps at 70% 1RM			
Shaw & Shaw 2005	India	Mean age = 28 yrs Male Healthy sedentary	8 weeks 3 d per week	Supervision not reported Free weights, weight machines and body weight 3 sets of 15 reps at 60% 1RM	Continued with habitual activity	Baseline and 8 weeks	Not reported
Shenoy et al. 2009	Canada	RT = 49.6 ± 5.2 yrs AT = 52.2 ± 9.3 yrs CON = 58.4 ± 1.8 yrs Male and female Type 2 diabetes	16 weeks 2 d per week	Supervision not reported Free weights, weight machines and body weight 3 sets of 10 reps	Usual care of continuing with habitual activity and medications	Baseline and 16 weeks	Grant from the University Grants Commission, New Delhi, India.
Sigal et al. 2009	Finland	RT = 54.7 ± 7.5 yrs AT = 53.9 ± 6.6 yrs Combined = 53.5 ± 7.3 yrs CON = 54.8 ± 7.2 yrs Male and female Type 2 diabetes	22 weeks 3 d per week	Supervised Weight machines 2-3 sets of 7-9 reps	Continued with habitual activity	Baseline, 12 and 24 weeks	Grants from the Canadian Institutes of Health Research (grant MCT-44155), the Canadian Diabetes Association, a New Investigator Award from the Canadian Institutes of Health Research, Career Scientist Award from the Ontario Ministry of Health and Long Term Care, a Postgraduate Scholarship from the National Sciences and Engineering Research Council, a New Investigator Award from the Heart and Stroke Foundation, Doctoral Research Award from the Social Sciences and Humanities Research Council and an Ontario Graduate Scholarship.
Sillanpaa et al. 2012 *Sillanpaa et al. 2009*	USA	RT = 54.2 ± 8.1 yrs AT = 53.7 ± 8.2 yrs Combined = 53.9 ± 8 yrs	21 weeks Endurance and strength - 2 d a week;	Supervised Free weights, weight machines and body weight 3-4 sets	Not reported	Baseline and 21 weeks	Supported, in part, by a grant from the Ministry of Education, Finland, the Central Finland Health Care District, Jyväskylä Finland, Juho Vainio Foundation, Finland, Sport

Sillanpaa et al. 2009		CON = 54.5 ± 9.1 yrs Male and female Healthy elderly *RT = 54.1 ± 6 yrs* *AT = 52.6 ± 7.9 yrs* *Combined = 56.3 ± 6.8 yrs* *CON = 53.8 ± 7.7 yrs* *Males* *RT = 50.8 ± 7.9 yrs* *AT = 51.7 ± 6.9 yrs* *Combined = 48.9 ± 6.8 yrs* *CON = 51.4 ± 7.8 yrs* *Female* *Healthy sedentary*	Combined 4 d a week	1-7 weeks: 15-20 reps at 40-60% 1RM 8-14 weeks: 10-12 reps at 60-80% 1RM 15-21 weeks: 6-8 reps at 70-80% 1RM			Institute Foundation, Finland and Yrjö Jahnsson Foundation, Finland.
Simons & Andel 2006	Canada	RT = 84.6 ± 4.5 yrs Walking = 81.6 ± 3.3 yrs CON = 84 ± 3.3 yrs Male and female Healthy elderly	16 weeks 2 d per week	Supervised Weight machines 1 set of 10 reps at 75% 1RM	Not reported	Baseline and 16 weeks	Not reported
Simpson et al. 1992	Korea	RT = 73 ± 4.8 yrs CON = 70 ± 5.7 yrs Male and female Chronic airflow limitation	8 weeks 3 d per week	Supervised Free weights and weight machines 3 sets of 10 reps at 50-85% 1RM	Not reported	Baseline and 8 weeks	Grants from the Medical Research Council of Canada, the Heart and Stroke Foundation of Ontario, and the Ontario Thoracic Society.
Song & Sohng 2012	Brazil	RT = 52.1 ± 12.4 yrs CON = 54.6 ± 10.1 yrs Male and female Haemodialysis	12 weeks 3 d per week	Supervised Free weights and elastic resistance bands 3 sets of 10-15 reps	Not reported	Baseline and 12 weeks	Not reported

Souza et al. 2013	UK	RT = 25.9 ± 6.4 yrs Interval Training = 24 ± 7.5 yrs CON = 22.5 ± 3.9 yrs Male Physically active	8 weeks 2 d a week	Supervision not reported Weight machines 1–2 weeks: 3 sets at 12RM 3–4 weeks: 4 sets at 8–10RM 5–6 weeks: 5 sets at 6–8RM 7–8 weeks: 3 sets at 10–12RM	Not reported	Baseline and 8 weeks	Grants from Fundação de Amparo á Pesquisa do Estado de São Paulo - 2007/02738-6, 2010/51428-2, 2009/03143-1 and Conselho Nacional de Desenvolvimento Científi co e Tecnológico (CNPq) – 152658/2011-4, 470207/2008-6 and 303162/2008-2.
Stebbings et al. 2013	Belgium	RT = 19 ± 3 yrs CON = 23 ± 2.4 yrs Male and female Physically active	8 weeks (4 weeks of detraining) 3 d per week	Supervision of 2 sessions a week Weight machines and body weight 3 sets of 10 reps at 80% 1RM	Continued with habitual activity	Baseline, 8, 10 and 12 weeks	Not reported
Stegen et al. 2015	Norway	RT = 54.8 ± 7.6 yrs AT = 54 ± 6.6 yrs CON = 54.6 ± 7.1 yrs Combined = 53.6 ± 7.2 yrs Male and female Type 2 diabetes	24 weeks 3 d per week	Supervised Biweekly supervision after week 4 Weight machines 2-3 sets if 7-9 reps	Continued with habitual activity and had the same level of contact from the research team as the exercise group	Baseline and 24 weeks	Grants from the Research Foundation- Flanders (FWO G.0243.11 and G.0352), Canadian Institutes of Health Research (Grant MCT-44155), the Canadian Diabetes Association, a Health Senior Scholar Award from Alberta Innovates-Health Solutions and a Research Chair from the University of Ottawa.
Stensvold et al. 2010	Norway	RT = 50.9 ± 7.6 yrs AT = 49.9 ± 10.1 yrs Combined = 52.9 ± 10.4 yrs CON = 47.3 ± 10.2 yrs Male and female Metabolic syndrome	12 weeks 3 d per week	Supervised Week 1: 60% 1RM 2-13 weeks: 3 sets of 8-12 reps at 80% 1RM	Continued with habitual activity	Baseline and 12 weeks	Supported by the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology.
Stensvold et al. 2012	Norway	RT = 50.9 ± 7.6 yrs AT = 49.9 ± 10.1 yrs CON = 47.3 ± 10.2 yrs Male and female Metabolic syndrome	13 weeks 4 d per week	Supervised Week 1: 60% 1RM 2-13 weeks: 3 sets of 8-12 reps at 80% 1RM	Not reported	1 and 12 weeks	Grants from Raagholts Foundation.

Strasser et al. 2009	Norway	RT = 74 ± 5 yrs AT = 76 ± 5 yrs CON = 74 ± 5 yrs Male and female Healthy elderly	24 weeks 3 d per week	Supervised Free weights, weight machines and body weight 3-6 sets (per week) of 10-15	Continued with habitual activity	Baseline and 24 weeks	Not reported
Tanimoto et al. 2009	Turkey	RT Low intensity = 19.0 ± 0.2 yrs RT High intensity = 19.5 ± 0.1 yrs CON = 19.8 ± 0.2 yrs Male Physically active	13 weeks 2 d per week	Supervision not reported RT Low intensity: 3 sets at 55-60% 1RM) RT High intensity: 3 sets at 85-90% 1RM	Continue with habitual activity	Baseline and 13 weeks	Not reported
Thabitha et al. 2012	India	Chronic obstructive pulmonary disease	3 d per week	Supervised Free weights and weight machines 1-3 sets of 10 reps		Baseline and endpoint (unknown)	Not reported
Tsutsumi et al. 1997	USA	RT high intensity/low volume = 67.8 ± 4.9 yrs RT low intensity/high volume = 68.9 ± 7.5 yrs CON = 69.8 ± 4.6 yrs Male Healthy elderly	12 weeks 3 d per week	Supervised RT high intensity/low volume: 8-12reps at 75-85% 1RM RT low intensity/high volume: 12-16 reps at 55-65% 1RM	Continued with habitual activity	Baseline and 12 weeks	Not reported
Van de Rest et al. 2014	Netherlands	Placebo: RT = 79.2 ± 6.3 yrs CON = 81.2 ± 7.4 yrs Protein: RT = 77.7 ± 8.8 yrs CON = 77.9 ± 8.1 yrs Male and female Healthy elderly	24 weeks 2 d per week	Supervised Weight machines 3-4 sets of 8-15 reps at 50-75% 1RM	Not reported	Baseline and 24 weeks	Funded by Top Institute Food and Nutrition and co-financed by the Dutch Dairy Association (NZO) and the European Union's Seventh Framework Program under Grant Agreement No. 266486.

Vatani et al. 2011	Iran	Moderate intensity = 20.8 ± 1.5 yrs High intensity = 19.9 ± 0.7 yrs CON = 20.9 ± 1.1 yrs Male Healthy sedentary	6 weeks 3 d per week	Supervision not reported Weight machines MI- 45-55% 1RM in 3 sets with 10-12 reps per set HI - 80-90% 1RM in 3 sets with 4-6 reps per set		Baseline and 6 weeks	Not reported
Venojarvi et al. 2013 *Venojarvi et al. 2013*	Finland	RT = 54 ± 6.1 yrs Nordic walking = 55 ± 6.2 yrs CON = 54 ± 7.2 yrs *RT = 54 ± 1.1 yrs* *Nordic walking = 55 ± 1 yrs* *CON = 54 ± 1 yrs* Male Sedentary obese	13 weeks 4 d per week *12 weeks* *3 d per week*	Supervised Free weights and weight machines 5RM	Continued with habitual activity	Baseline and 12 weeks	Grants from the Research Council for Physical Education and Sports, the Finnish Ministry of Education, and Turku University of Applied Sciences R&D program. *Grants from the Research Council for Physical Education and Sports, of the Finnish Ministry of Education, Turku University of Applied Sciences R&D program and the COST action CM1001.*
Vincent et al. 2002 *Vincent et al. 2003* *Vincent et al. 2003*	USA	LEX = 67.6 ± 6.3 yrs HEX = 66.6 ± 6.7 yrs CON = 71 ± 4.7 yrs *LEX = 67.4 ± 7 yrs* *HEX = 66.5 ± 7 yrs* *CON = 71.1 ± 5 yrs* *LEX = 67.6 ± 6 yrs* *HEX = 66.6 ± 7 yrs* *CON = 71.1 ± 5 yrs* Male and female Healthy elderly	24 weeks 3 d per week	Supervised Weight machines LEX – 1 set of 13 reps at 50% 1RM HEX – 1 set of 8 reps at 80% 1RM *Supervision not reported*	Continued with habitual activity	Baseline and 24 weeks	Not reported
Vincent et al. 2006	USA	Normal weight: RT = 68.1 ± 1.5 yrs	24 weeks 3 d per week	Supervision not reported Weight machines 1 set of 8-13 reps at 50-80% 1RM	Continued with habitual activity	Baseline and 24 weeks	Supported, in part, by Grants T32-AT00052 and K30-AT-00,060 from the National Centre for

		CON = 70.9 ± 1.4 yrs Overweight/obese: RT = 66.5 ± 1.2 yrs CON = 71.2 ± 2.1 yrs Male and female Sedentary obese					Complementary and Alternative Medicine.
Vona et al. 2009	Switzerland	RT = 57 ± 8 yrs AT = 56 ± 6 yrs Combined = 55 ± 9 yrs CON = 58 ± 7 yrs Male and female Cardiac rehabilitation	4 weeks 4 d per week	Supervision not reported Free weights and elastic resistance bands 4 sets of 10-12 reps at 60% 1RM	Continued with habitual activity	Baseline and 4 weeks	Not reported
Wanderley et al. 2013	Portugal	RT = 67.3 ± 4.9 yrs AT = 69.9 ± 5.7 yrs CON = 67.8 ± 5.5 yrs Male and female Healthy elderly	32 weeks 3 d per week	Supervised Weight machines 2 sets of 12-15 reps at 50-60%1RM progressing to 80% 1RM at week 4	Continued with habitual activity	Baseline and 32 weeks	Supported by the Portuguese Foundation for Science and Technology (grant numbers, PTDC/DES/108780/2008 and SFRH/BD/33124/2007).
Weiser & Haber 2007	Austria	RT = 76.1 ± 2.9 yrs CON = not reported Male and female Healthy elderly	12 weeks 2 d per week	Supervision not reported Free weights, weight machines and body weight 1-4 weeks: 1 set of 10-15 reps 5-8 weeks: 3 sets of 10-15 reps 9-12 weeks: 4 sets of 10-15 reps	Not reported	Baseline and 12 weeks	Not reported
Wiles et al. 2010	UK	18-34 years Male Physically active	8 weeks 3 d per week	Supervision not reported Isometric exercise 75% and 95% peak heart rate	Not reported	Baseline, 4 and 8 weeks	Not reported
Yavari et al. 2012	Iran	RT = 51.5 ± 6.3 yrs AT = 48.2 ± 9.2 yrs Combined = 50.9 ± 9.8 yrs CON = 51.5 ± 8.5 yrs Sex not reported Type 2 diabetes	52 weeks 2-3 d per week	Supervised Weight machines 1-4 weeks: 1-2 sets of 8-10 reps at 60% 1RM 4-52 weeks: 3 sets of 8-10 reps at 75-80% 1RM	Continued with habitual activity	Baseline and 52 weeks	Grant from the Tabriz University of Medical Sciences and with a co-operation of Endocrinology Reasearch Centre of Emam Reza haspital (Tabriz University of Medical Sciences).

Yoshizawa et al. 2009	Japan	RT = 47 ± 2 yrs AET = 47 ± 2 yrs CON = 49 ± 3 yrs Female Healthy sedentary	12 weeks 2 d per week	Supervision not reported Weight machines 3 sets of 10 reps at 60% 1RM.	Not reported	Baseline and 12 weeks	Supported by a Grant for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (18300215, 18650186, 21970), and Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan.
Zambom-Ferraresi et al. 2015	Spain	RT = 68 ± 7 yrs RT + AT = 68 ± 7 yrs CON = 69 ± 5 yrs Male Chronic obstructive pulmonary disease	6 weeks 2 d per week	Supervision not reported Weight machines 3-4 sets of 6-12 reps at 50-70% 1RM	Not reported	Baseline and 6 weeks	Support from the Spanish Ministry of Education and Science (Plan Nacionall + D + i 2004-2007 Strategic action: “Sport and physical education” Ref: DEP2007-73220), Health Sciences Department of Government of Navarre. F and a pre-doctoral fellowship from the Public University of Navarre.
Zavanela et al. 2012	Brazil	Age not reported Male Healthy sedentary	24 weeks 3-4 d per week	Supervised Free weights and weight machines 3 sets of 10–12 reps at 10–12RM	Continued with habitual activity	Baseline and 24 weeks	Not reported

Appendix 2c. *Populations used in the Included Studies*

	Population	Number	Percent
Healthy	Sedentary men and women	46	25.6
	Elderly men and women	30	16.7
	Physically active adults aged 18-35 years	20	11.1
	Postmenopausal women	5	2.8
Clinical			
Cardiac	Pre-hypertensive and newly diagnosed/never-treated hypertensive	3	1.7
	Coronary bypass graft	1	0.6
	Stable coronary heart failure	1	0.6
	Cardiac rehabilitation	1	0.6
Cancer	Breast cancer	3	1.7
	Disseminated germ cell cancer	1	0.6
	Prostate cancer	1	0.6
Non-cancer	Type 2 diabetes	18	10
	Sedentary obese/overweight	14	7.8
	Metabolic risk factors or syndrome	5	2.8
	Peripheral artery disease	4	2.2
	Chronic obstructive pulmonary disease	4	2.2
	Kidney transplant	3	1.7
	Musculoskeletal (e.g. osteoporosis, osteopenia or osteoarthritis	2	1.1
	Haemodialysis	2	1.1
	Non-alcoholic fatty liver disease	2	1.1
	Polycystic ovary syndrome	1	0.6
	HIV/AIDS	1	0.6
	Trapezius myalgia	1	0.6
	Total hip arthroplasty	1	0.6
	Chronic lumbar pain	1	0.6
	Cystic fibrosis	1	0.6
	Young men with depression/anxiety	1	0.6
	Impaired glucose tolerance	1	0.6
	Chronic airflow limitation	1	0.6

Appendix 2d. *Risk of Bias Assessment*

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Ades et al. 1996	?	?	+	?	-	-
Afshar et al. 2010	?	?	+	?	-	-
Ahmadizad et al. 2007	?	?	+	?	-	+
Ahmadizad et al. 2014	?	?	+	?	-	-
Almenning et al. 2015	-	?	+	+	-	-
Anderson et al. 2004	?	?	+	?	-	-
Andersen et al. 2008	?	?	+	?	?	+
Andersen et al. 2014	?	?	+	?	-	?
Andersen et al. 2016	-	?	+	-	-	-
Arora et al. 2009	?	?	+	?	-	-
Asad et al. 2012	?	?	+	?	-	+
Augusto Libardi et al. 2012	?	?	+	?	-	-
Azarbayjani et al. 2014	?	?	+	?	+	-
Badrov et al. 2013	-	-	+	?	-	-
Baldi and Snowling 2003	?	?	+	?	-	-
de Barros et al. 2010	-	-	+	-	-	-
Beck et al. 2013	-	?	+	?	-	-
Bell et al. 2000	?	?	+	?	-	-
Beltran Valls et al. 2014	?	?	+	?	-	-
Bertuzzi et al. 2013	-	?	+	?	?	-
Bishop and Jenkins 1996	?	?	+	?	-	-
Bishop et al. 1999	?	?	+	?	-	-
Boardley et al. 2007	+	+	+	?	+	-
Borges and Carvalho 2014	?	?	+	?	+	-
Brentano et al. 2008	?	?	+	?	-	-
Brito et al. 2013	?	-	+	?	-	-
Broeder et al. 1992	?	?	+	?	+	-
Brooks et al. 2007	?	?	+	-	-	-
Buchner et al. 1997	+	?	+	-	-	-
Camargo et al. 2008	?	?	+	-	-	-
Castaneda et al. 2002	?	?	+	?	-	-
Christensen et al. 2014	-	-	+	+	-	-
Colado et al. 2009	?	?	+	-	?	-
Conceição et al. 2013	?	?	+	?	-	-
Courneya et al. 2007	-	-	+	?	-	-
Croymans et al. 2013	-	?	+	-	-	-
Davidson et al. 2009	?	?	+	-	-	-
de Lima et al. 2012	?	?	+	?	-	-
De Souza et al. 2014	?	?	+	?	-	-
DeVallance et al. 2016	-	?	+	-	-	-
Deibert et al. 2011	?	?	+	?	-	-
Donges et al. 2010	+	?	+	?	-	-

Dunstan et al. 1998	?	?	+	?	?	-
Edge et al. 2006	?	?	+	?	-	-
Egana et al. 2010	?	?	+	?	-	-
Elliott et al. 2002	?	?	+	?	-	-
Fahlman et al. 2002	?	?	+	?	-	-
Fatouros et al. 2005	?	?	+	?	-	-
Fenkci et al. 2006	?	?	+	?	-	-
Figueroa et al. 2012	?	?	+	?	?	-
Franklin et al. 2015	?	?	+	?	-	-
Garcia-Lopez et al. 2007	?	?	+	?	-	-
Gater et al. 1992	?	?	+	?	?	-
Gelecek et al. 2012	-	?	+	-	-	-
Gettman et al. 1978	?	?	+	?	+	-
Gordon et al. 2006	?	?	+	?	-	-
Greenwood et al. 2015	-	?	+	-	+	-
Gregory et al. 2013	?	?	+	?	-	-
Hagberg et al. 1989	?	?	+	?	-	-
Hagerman et al. 2000	?	?	+	?	?	-
Hagstorm et al. 2016	-	?	+	-	-	-
Hallsworth et al. 2011	?	?	+	?	-	-
Hautala et al. 2006	?	?	+	?	+	-
Haykowsky 2000	?	?	+	?	-	-
Haykowsky 2005	?	?	+	?	?	-
Hedayati 2012	?	?	+	?	-	-
Heffernan 2013	?	?	+	?	?	-
Hendrickson 2012	?	?	+	?	-	-
Hiatt 1994	?	?	+	?	?	-
Holviala et al. 2012	?	?	+	?	-	-
Hoff 2007	?	?	+	?	?	-
Hoof et al. 1996	?	?	+	?	+	-
Horne et al. 1996	?	?	+	?	-	-
Hu et al. 2009	?	?	+	?	-	-
Huffman et al. 2014	-	?	+	?	-	-
Husby et al. 2009	-	-	+	?	-	-
Irving et al. 2015	?	?	+	?	-	-
Jay et al. 2011	-	?	+	-	-	-
Kaikkonen et al. 2000.	?	?	+	?	-	-
Kanegusuku et al. 2011	?	?	+	?	-	-
Karavirta et al. 2009	?	?	+	?	-	-
Karavirta et al. 2013	?	?	+	?	?	-
Karelis et al. 2016	-	-	+	?	-	-
Kawano et al. 2006	?	?	+	?	-	-
Kell and Asmundson 2009	?	?	+	?	-	-
Kemi et al. 2011	?	?	+	?	-	-
Kemmler et al. 2016	-	?	+	-	-	-
Khorvash et al. 2012	?	?	+	?	+	?
Kim et al. 2011	?	?	+	?	-	-
Kriemler et al. 2013	+	?	+	+	-	-
Ku et al. 2010	?	?	+	?	-	-
Kwon et al. 2010	?	?	+	?	+	-
Kwon et al. 2011	?	?	+	?	-	-
Larose et al. 2010	?	?	+	?	-	-
LeMura et al. 2000	?	?	+	?	-	-

Levinger et al. 2007	?	?	+	?	-	-
Libardi et al. 2011	?	?	+	?	-	-
Lo et al. 2011	?	?	+	?	?	-
Lovell et al. 2009	-	?	+	-	-	-
Madden et al. 2006	?	?	+	?	?	-
Mahdirejei et al. 2014	?	?	+	?	-	-
Maiorana et al. 1997	?	?	+	?	-	-
Maiorana et al. 2011	?	?	+	?	-	-
Malin et al. 2013	?	?	+	?	-	-
Manning et al. 1991	?	?	+	?	-	-
Marcinik et al. 1991	?	?	+	?	-	-
Marcus et al. 2009	?	?	+	?	-	-
Martins et al. 2010	?	?	+	?	-	-
McDermott et al. 2009	-	?	+	-	-	-
McGuigan et al. 2001	?	?	+	?	?	-
Mikesky et al. 1994	+	?	+	?	-	-
Miller et al. 2008	?	?	+	?	-	-
Miura et al. 2008	?	?	+	?	-	-
Miyachi et al. 2004	?	?	+	?	-	-
Mosti et al. 2013	?	?	+	?	-	-
Mosti et al. 2014	-	?	+	?	-	-
Mota et al. 2013	+	+	+	?	-	-
Nikseresht et al. 2014	?	?	+	?	-	-
Nybo et al. 2010	+	+	+	?	-	-
O'Connor et al. 2017	-	-	+	-	?	-
Okamoto et al. 2006	?	?	+	-	-	-
Okamoto et al. 2009a	?	?	+	-	-	-
Okamoto et al. 2009b	?	?	+	?	-	-
Okamoto et al. 2011	?	?	+	-	-	-
Okamoto et al. 2013	?	?	+	?	-	-
Oldervoll et al. 2001	+	?	+	?	?	-
Oliveira et al. 2013	?	?	+	?	-	-
Olson et al. 2006	?	?	+	?	-	-
Osteras et al. 2002	?	?	+	?	-	-
Panton et al. 1990	?	?	+	?	-	-
Parr et al. 2009	-	?	+	?	-	-
Perez-Gomez et al. 2013	?	?	+	?	-	-
Plotnikoff et al. 2010	-	-	+	?	-	-
Poehlman et al. 2000	?	?	+	?	?	-
Poehlman et al. 2002	?	?	+	?	?	-
Pollock et al. 1991	?	?	+	?	-	-
Prabhakaran et al. 1999	?	?	+	?	-	-
Rana et al. 2008	?	?	+	?	?	-
Roberts et al. 2013	?	?	+	?	+	-
Rodriguez-Miguelez et al. 2014	?	?	+	?	?	-
Romero-Areanas et al. 2013	?	?	+	?	?	-
Sallinen et al. 2007	?	?	+	?	-	-
Sawyer et al. 2014	?	?	+	?	?	-
Schiffer et al. 2011	?	?	+	?	?	-
Schmidt et al. 2014	?	?	+	-	-	-
Schmitz et al. 2002	?	?	+	-	-	?
Schmitz et al. 2005	-	-	+	-	-	-
Segal et al. 2009	-	-	+	?	-	-

Shamsoddini et al. 2015	?	?	+	?	?	-
Shaw and Shaw 2005	-	?	+	?	?	-
Shenoy et al. 2009	?	?	+	?	-	-
Sigal et al. 2009	-	-	+	-	-	-
Sillanpaa et al. 2012	-	?	+	?	?	-
Simons and Andel 2006	?	?	+	-	-	-
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Song and Sohng 2012	?	?	+	?	-	-
Souza et al. 2013	?	?	+	?	?	-
Stebbings et al. 2013	?	?	+	-	?	-
Stegen et al. 2015	?	?	+	?	-	-
Stensvold et al. 2010	-	?	+	?	-	-
Stensvold et al. 2012	-	?	+	?	-	-
Storen et al. 2008	?	?	+	?	-	-
Strasser et al. 2009	-	?	+	?	?	-
Sunde et al. 2010	?	?	+	?	-	-
Tanimoto et al. 2009	?	?	+	?	-	-
Thabitha et al. 2012	?	?	+	?	?	-
Tsutsumi et al. 1997	?	?	+	?	-	-
Van de Rest et al. 2014	-	-	+	?	-	?
Vatani et al. 2011	?	?	+	?	?	-
Venojarvi et al. 2013	?	?	+	?	?	-
Vincent et al. 2002	?	?	+	?	?	-
Vincent et al. 2006	?	?	+	?	?	-
Vona et al. 2009	?	?	+	?	-	-
Wanderley et al. 2013	-	?	+	?	+	-
Weiser and Haber 2007	-	?	+	?	?	-
Wiles et al. 2010	-	?	+	?	?	-
Yavari et al. 2012	?	?	+	?	+	-
Yoshizawa et al. 2009	?	?	+	?	-	-
Zambom-Ferraresi et al. 2015	-	?	+	-	-	-
Zavanela et al. 2012	?	?	+	?	?	-

Appendix 2e. *Publication Bias*

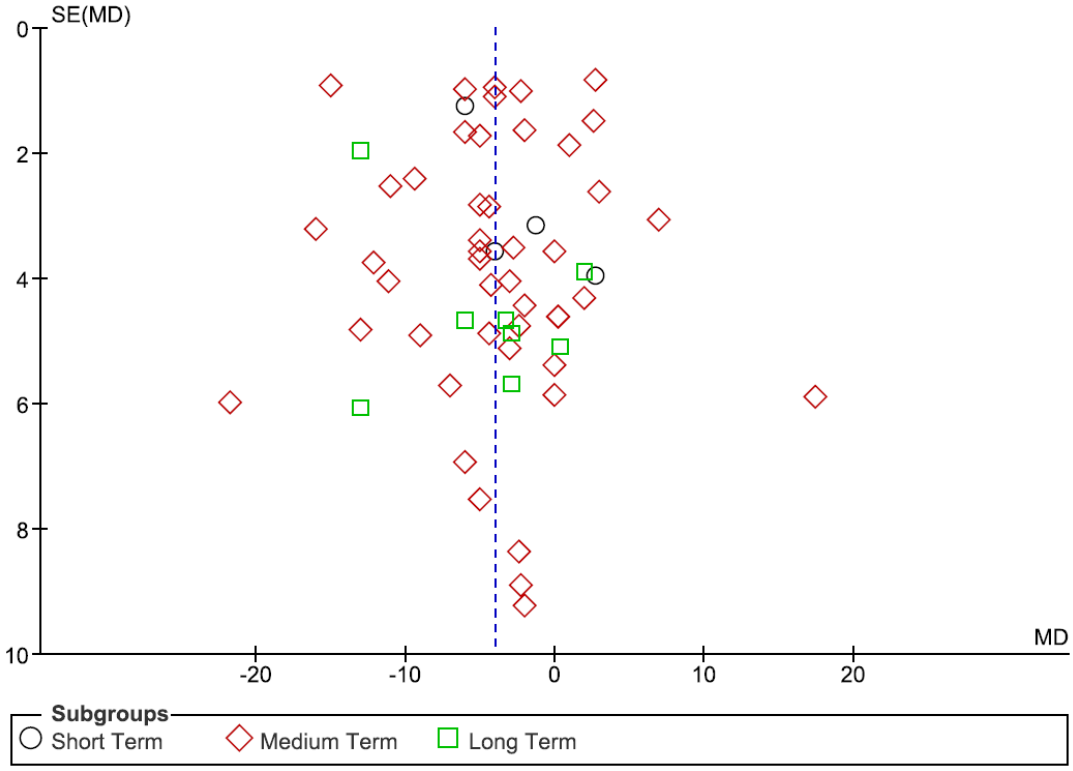


Fig 1. Funnel plot of studies reporting systolic blood pressure.

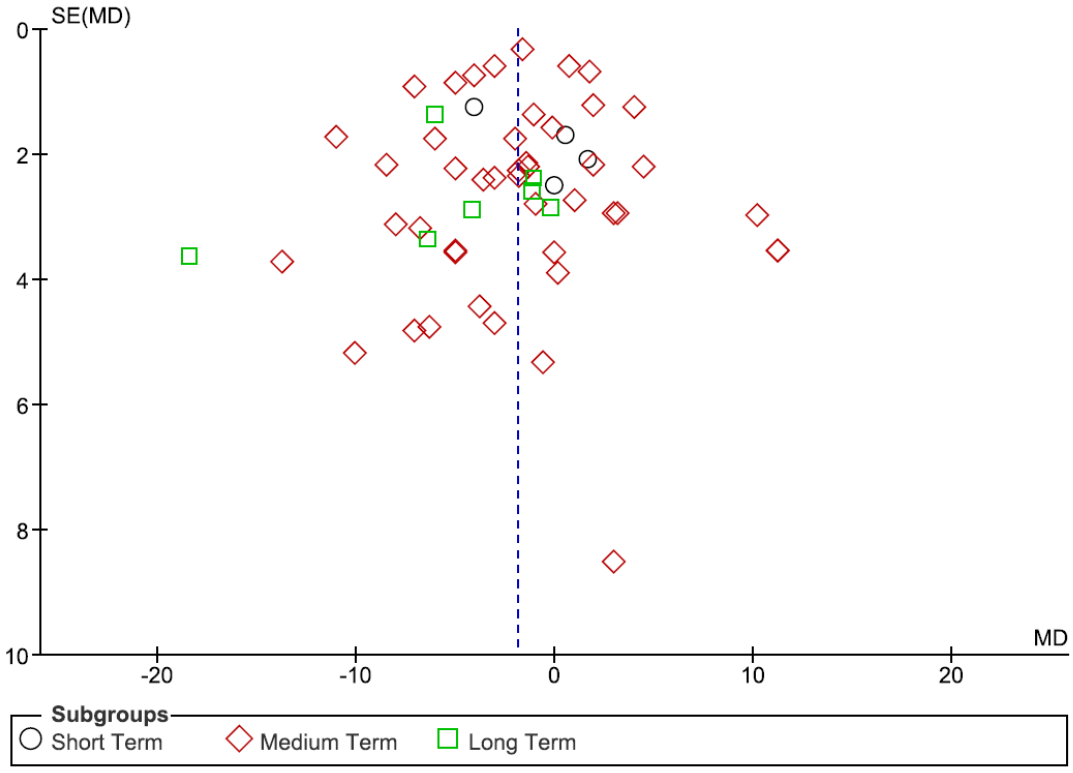


Fig 2. Funnel plot of studies reporting diastolic blood pressure.

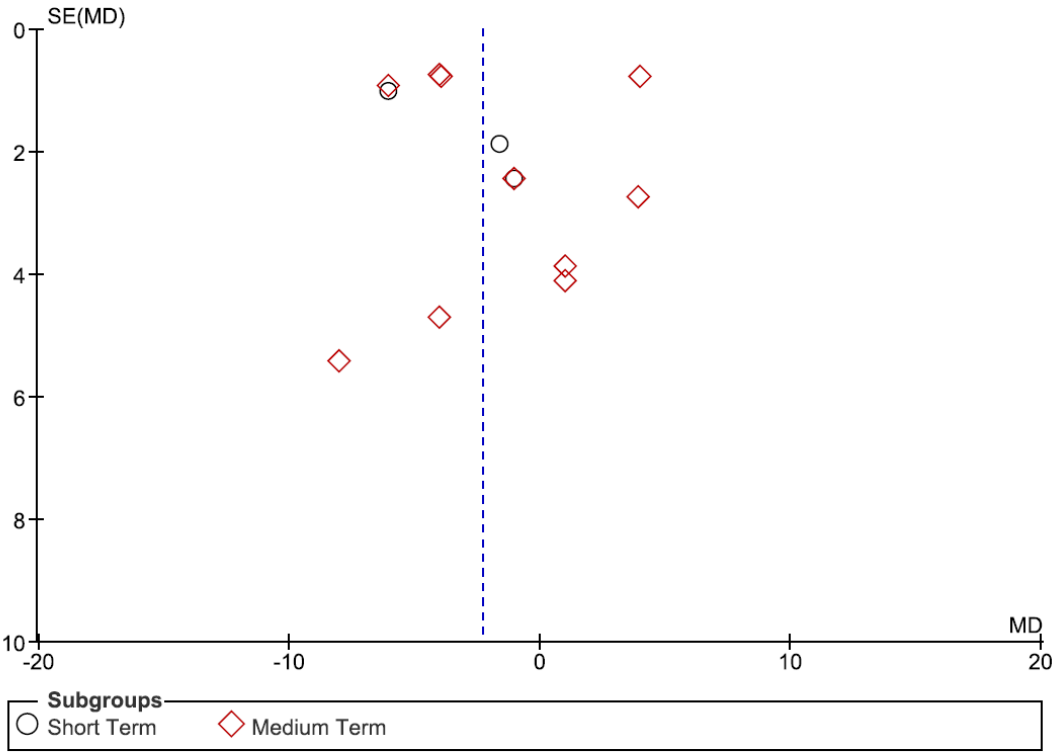


Fig 3. Funnel plot of studies reporting mean arterial pressure.

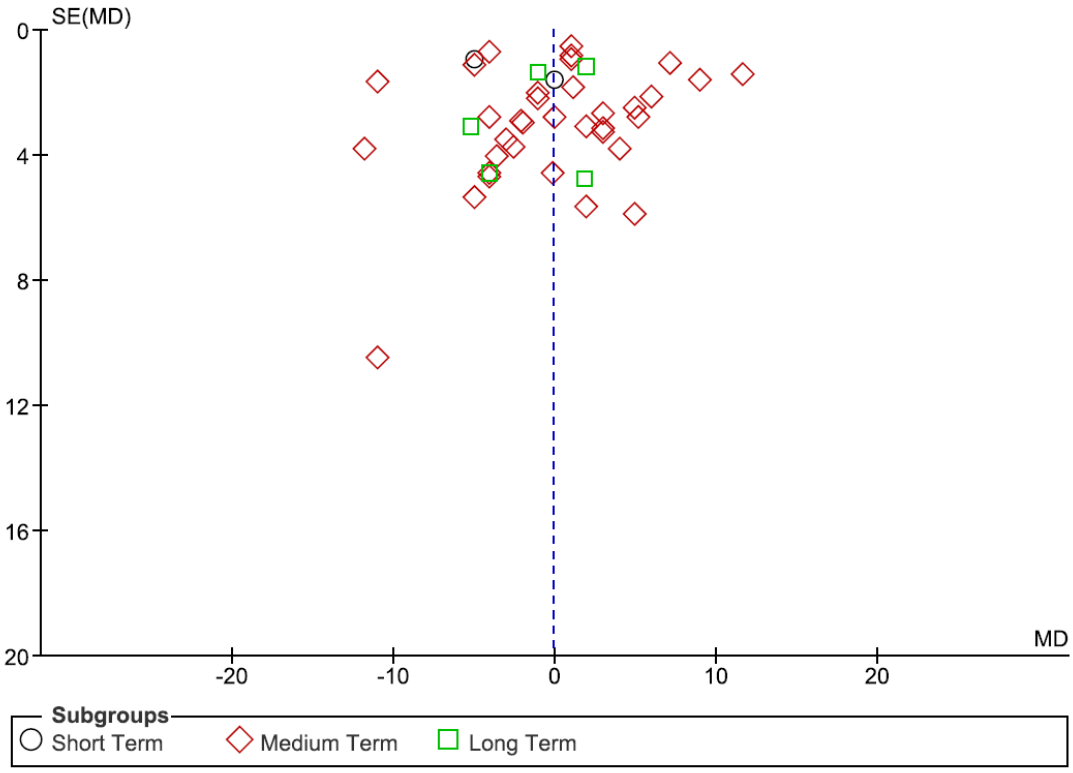


Fig 4. Funnel plot of studies reporting resting heart rate.

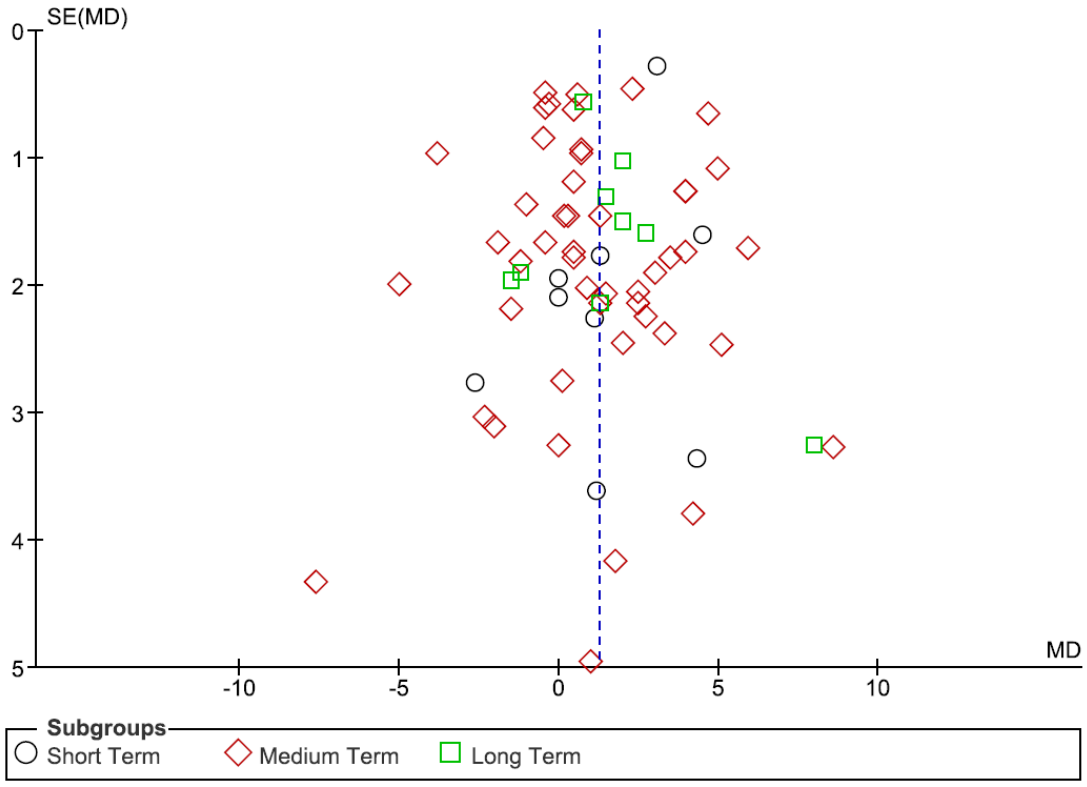


Fig 5. Funnel plot of studies reporting $\dot{V}O_2max$.

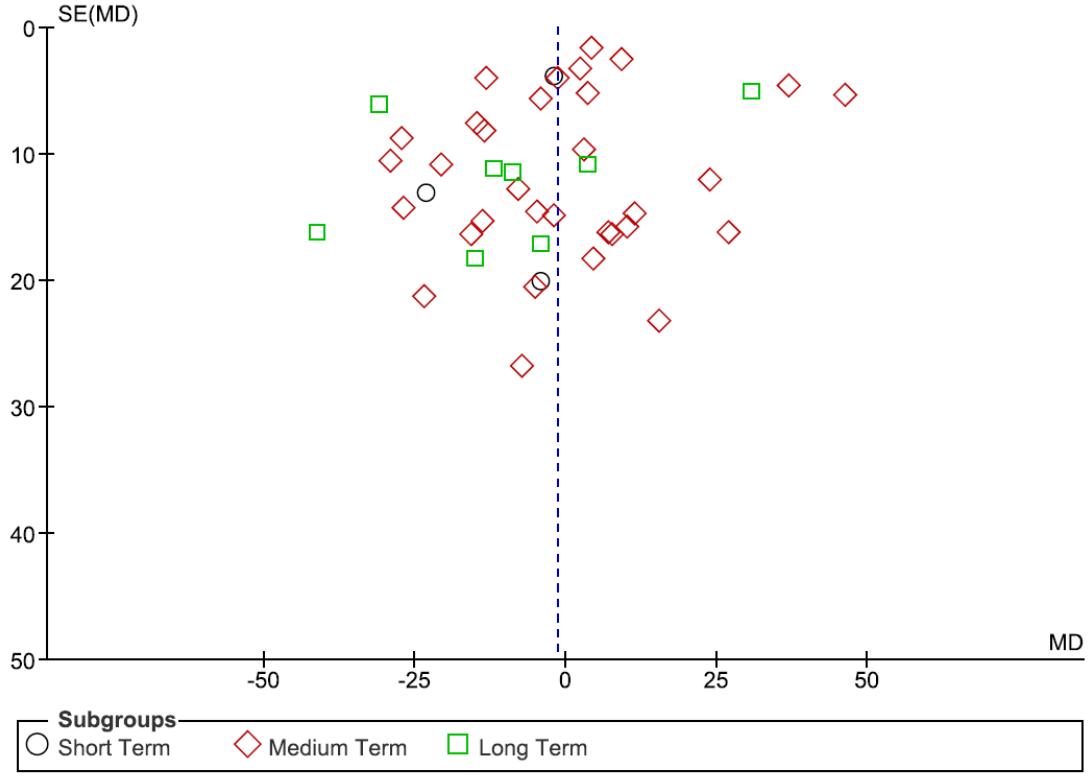


Fig 6. Funnel plot of studies reporting total cholesterol levels.

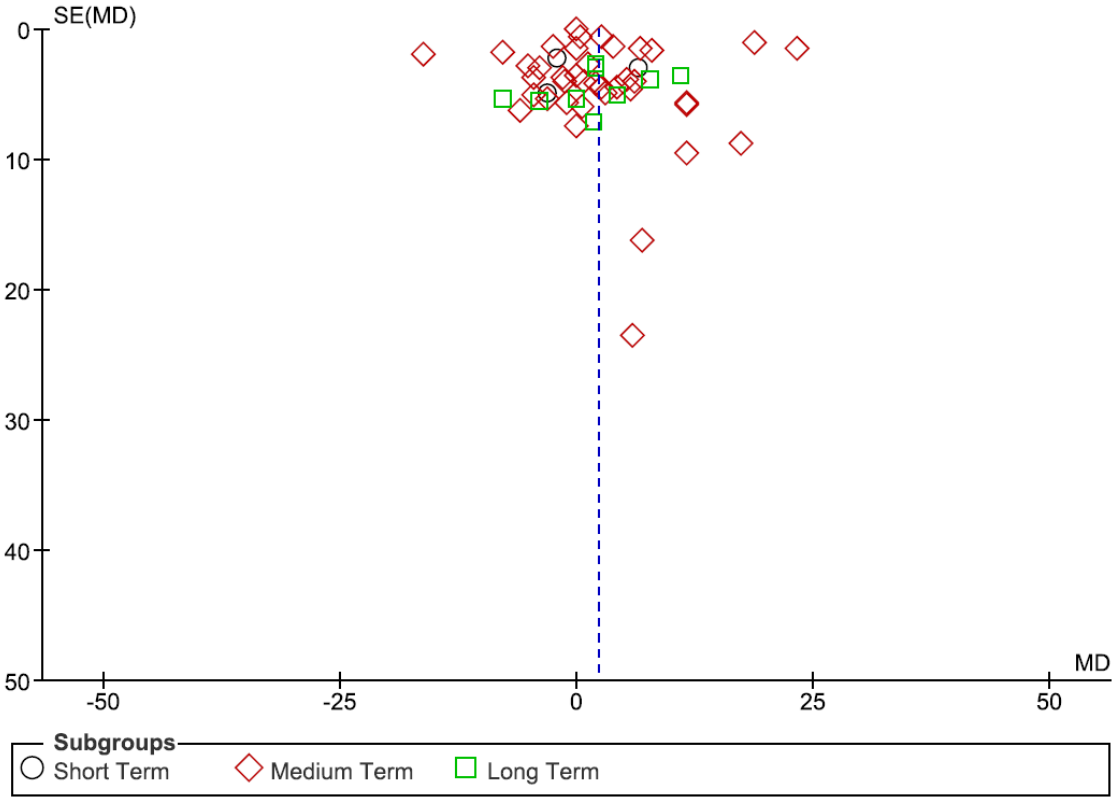


Fig 7. Funnel plot of studies reporting high density lipoprotein cholesterol levels.

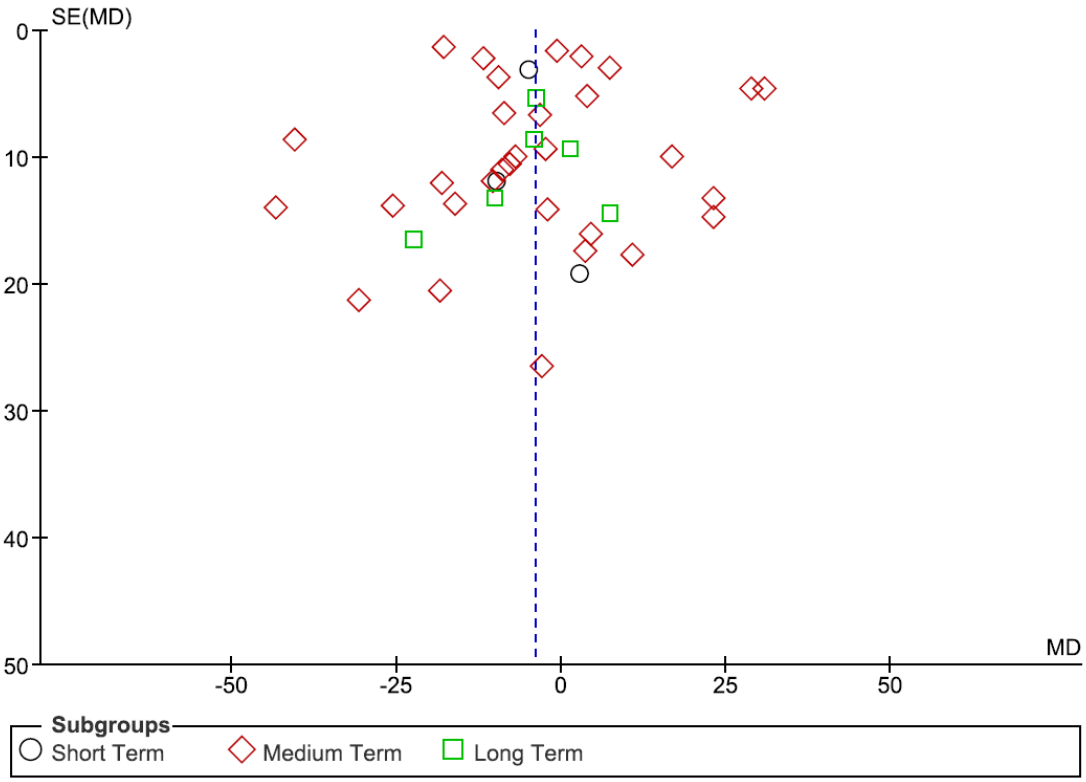


Fig 8. Funnel plot of studies reporting low density lipoprotein cholesterol levels.

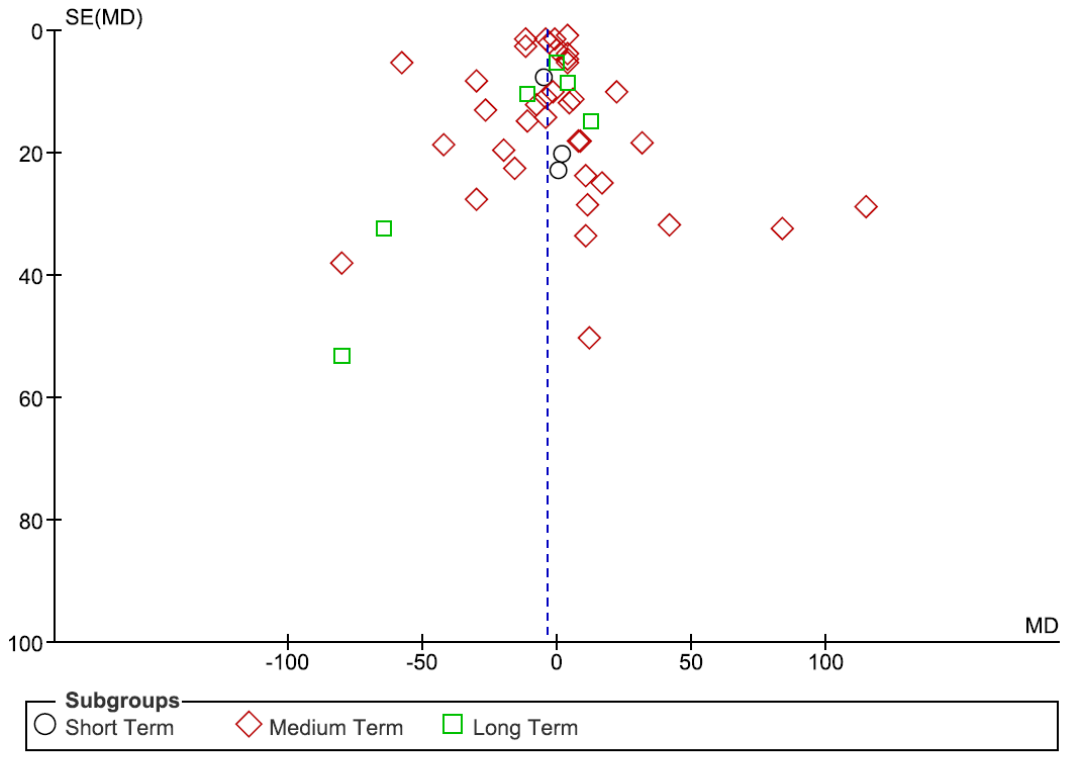


Fig 9. Funnel plot of studies reporting triglyceride levels.

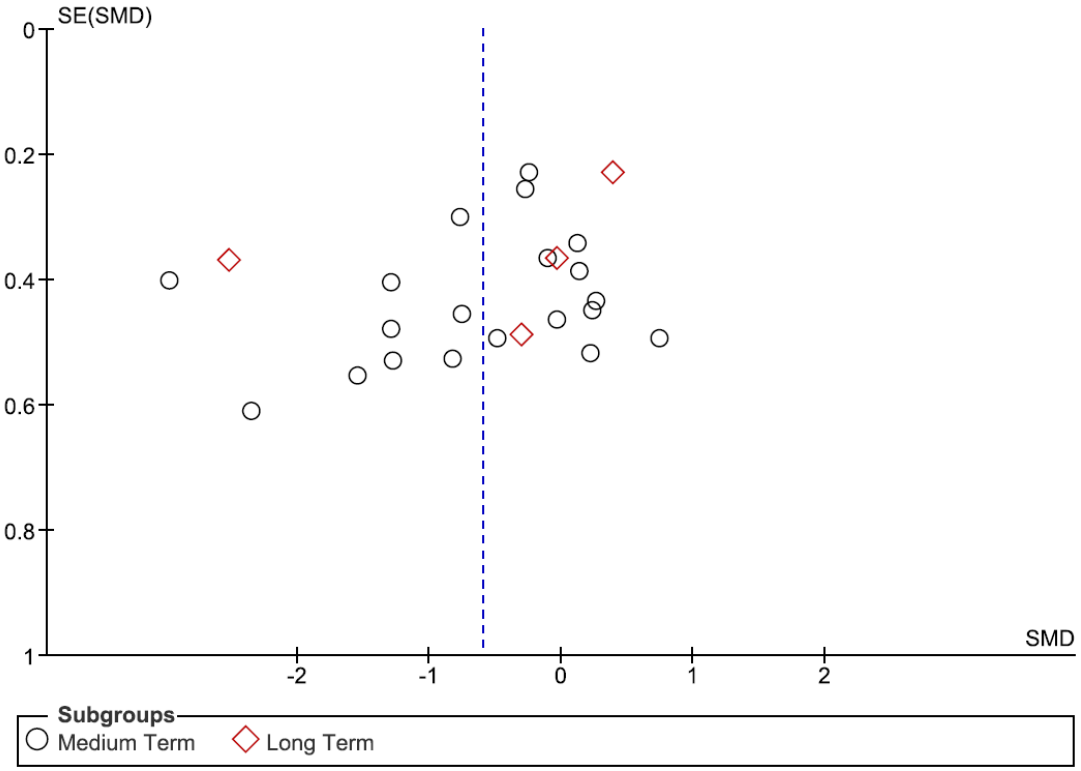


Fig 10. Funnel plot of studies reporting fasted insulin levels.

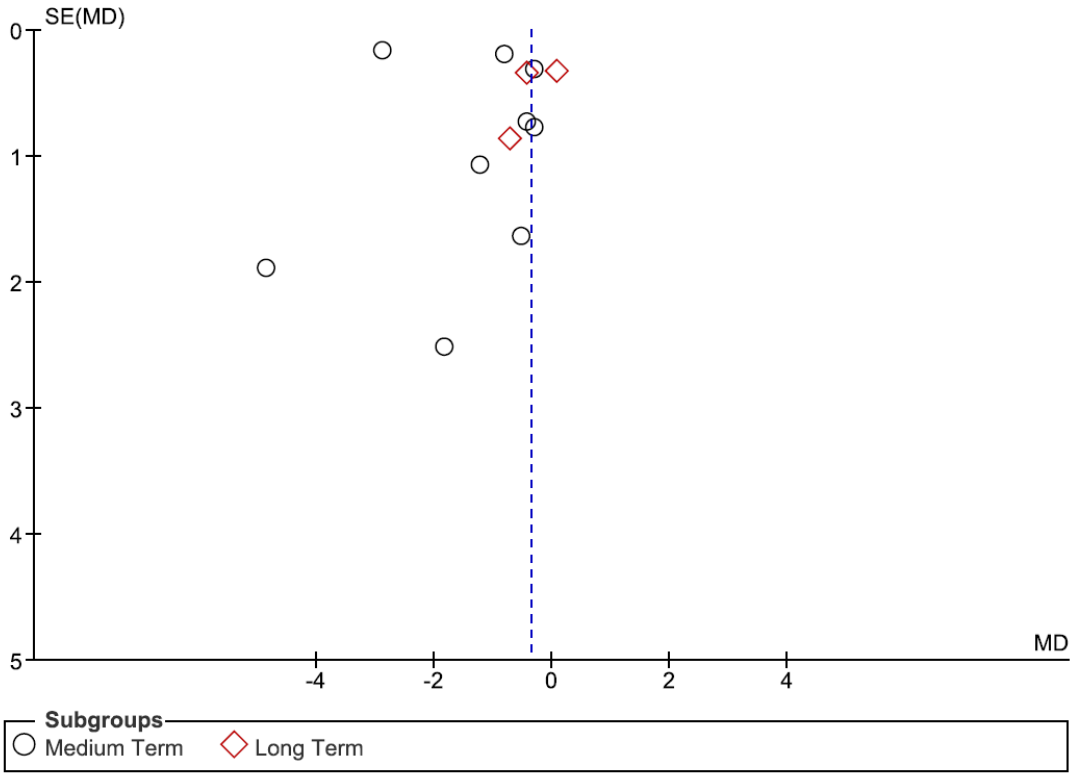


Fig 11. Funnel plot of studies reporting insulin resistance (HOMA-IR).

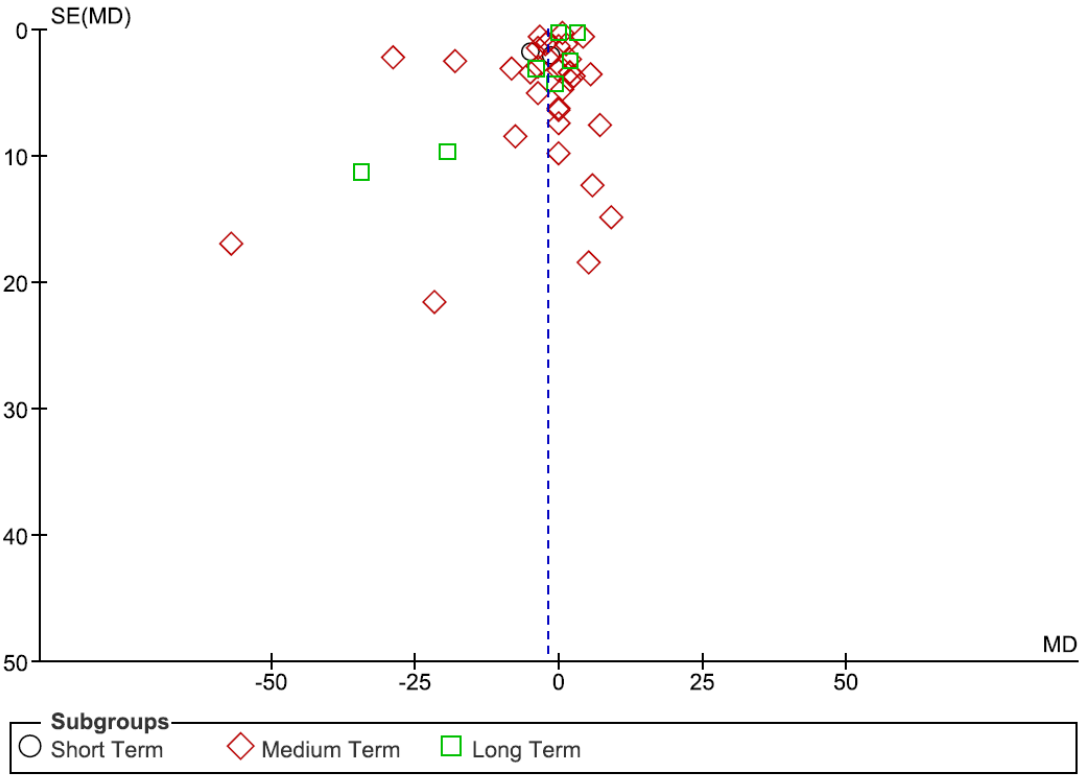


Fig 12. Funnel plot of studies reporting fasted glucose levels.

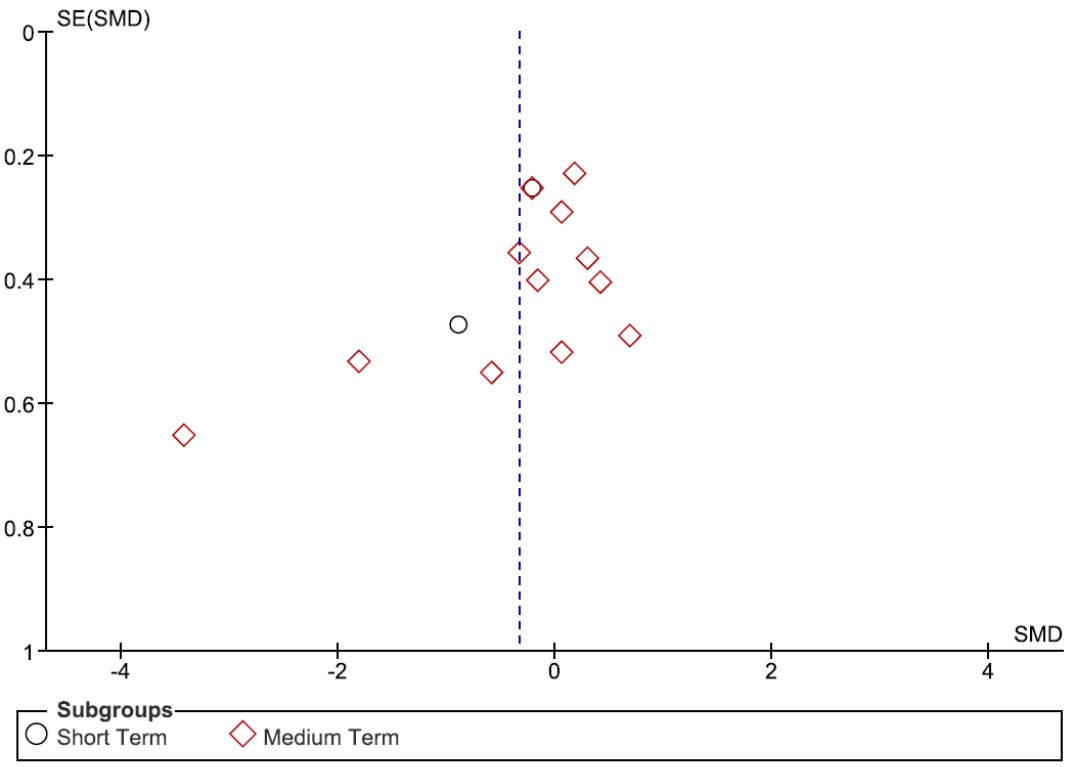


Fig 13. Funnel plot of studies reporting c-reactive protein levels.

Appendix 2f. *Sensitivity Analysis of the short- (ST), medium- (MT) and long-term (LT) effects of RET on cardiometabolic outcomes.*

Outcome		Number of studies	Number of participants		Mean difference [95% CI]	P values	Heterogeneity
			RT	CON			
SBP (mmHg)	*ST*	2	22	20	-2.49 [-7.14, 2.16]	0.29	χ^2 = 0.32, I² = 0%, P = 0.27 *
	MT	39	607	572	-4.14 [-6.36, -1.92]	0.0003	χ^2 = 301.18, I² = 87%, P < 0.00001
	LT	5	151	135	-3.88 [-11.18, 3.42]	0.3	χ^2 = 17.62, I² = 77%, P = 0.001
DBP (mmHg)	*ST*	2	22	20	0.41 [-2.36, 3.18]	0.77	χ^2 = 0.04, I² = 0%, P = 0.84 *
	MT	38	597	564	-1.86 [-3.19, -0.52]	0.006	χ^2 = 231.14, I² = 84%, P < 0.00001
	LT	5	138	138	-3.99 [-6.34, -1.64]	0.0009	χ^2 = 5.29, I² = 24%, P = 0.26 *
MAP (mmHg)	*ST*	2	22	20	-1.38 [-4.30, 1.54]	0.35	χ^2 = 0.04, I² = 0%, P = 0.85 *
	MT	9	128	125	-1.22 [-4.34, 1.90]	0.44	χ^2 = 95.95, I² = 92%, P < 0.00001
Resting Heart Rate (bpm) † §	*MT*	30	450	414	0.91 [-0.99, 2.81]	0.35	χ^2 = 236.88, I² = 88%, P < 0.00001
FMD (%)		6	68	70	1.69 [0.97, 2.41]	< 0.0001	χ^2 = 0.72, I² = 0%, *P* = 0.98
$\dot{V}O_2$max (ml/kg/min)	*ST*	7	159	115	1.52 [-0.13, 3.17]	0.07	χ^2 = 10.10, I² = 41%, *P* = 0.12
	MT	36	631	568	1.25 [0.45, 2.05]	0.002	χ^2 = 119.6, I² = 71%, P < 0.00001
	LT	6	128	101	1.82 [0.60, 3.04]	0.003	χ^2 = 0.6, I² = 0%, *P* = 0.99 *
Total Cholesterol (mg/dL)	*ST*	2	70	56	-2.07 [-9.62, 5.47]	0.59	χ^2 = 0.01, I² = 0%, P = 0.92 *
	MT	26	336	325	-3.78 [-9.12, 1.57]	0.17	χ^2 = 66.33, I² = 62%, P < 0.0001 *
	LT	4	56	52	-6.31 [-18.30, 5.68]	0.3	χ^2 = 1.34, I² = 0%, P = 0.72 *
HDL-chol (mg/dL)	*ST*	2	70	56	-2.17 [-6.26, 1.91]	0.3	χ^2 = 0.03, I² = 0%, P = 0.86 *
	MT	33	495	475	2.64 [-1.03, 6.31]	0.16	χ^2 =563.25, I² = 94%, P < 0.00001 *
	LT	5	120	115	0.80 [-3.07, 4.66]	0.12	χ^2 = 3.12, I² = 0%, P = 0.54 *
LDL-chol (mg/dL)	*ST*	2	70	56	-4.78 [-10.98, 1.42]	0.13	χ^2 = 0.17, I² = 0%, P = 0.68
	MT	25	397	382	-7.17 [-13.24, -1.09]	0.02	χ^2 = 147.44, I² = 84%, P < 0.00001 *
	LT	4	109	96	-3.97 [-11.86, 3.92]	0.32	χ^2 = 1.57, I² = 0%, P = 0.67
Triglycerides (mg/dL)	*ST*	2	70	56	-4.36 [-19.10, 10.37]	0.56	χ^2 = 0.06, I² = 0%, P = 0.81
	MT	32	492	471	-5.06 [-10.64, 0.53]	0.08	χ^2 = 233.71, I² = 87%, P < 0.00001
	LT	4	109	96	0.19 [-7.78, 8.16]	0.96	χ^2 = 1.93, I² = 0%, P = 0.59 *
Fasted insulin (µU/ml)	*MT*	16	246	226	-1.52 [-2.66, -0.39]	0.009	χ^2 = 47.11, I² = 66%, P < 0.0001 *
	LT	4	89	90	-0.60 [-1.93, 0.72]	0.37	χ^2 = 45.43, I² = 93%, P < 0.00001
HOMA-IR	*MT*	9	86	78	-1.40 [-2.58, -0.22]	0.02	χ^2 = 74.57, I² = 91%, P < 0.00001 *
	LT	3	38	33	-0.18 [-0.64, 0.27]	0.6	χ^2 = 1.45, I² = 0%, P = 0.48
Fasted glucose (mg/dL)	*ST*	2	64	58	-3.39 [-6.90, 0.11]	0.06	χ^2 = 1.66, I² = 40%, P = 0.2
	MT	27	410	397	-2.91 [-5.34, -0.47]	0.02	χ^2 = 310.64, I² = 91%, P < 0.00001
	LT	5	109	102	0.96 [-1.45, 3.38]	0.43	χ^2 = 31.42, I² = 87%, P < 0.00001
CRP (mg/L) †	*MT*	9	135	135	0.04 [-0.30, 0.38]	0.8	χ^2 = 7.59, I² = 0%, P = 0.47 *

† ST could not be calculated due to a lack of studies.
§ LT could not be calculated due to a lack of studies.
* Reduction in heterogeneity

Appendix 2g. *Short-, Medium-, Long-term Effects of Resistance Exercise Training on Study Outcomes*

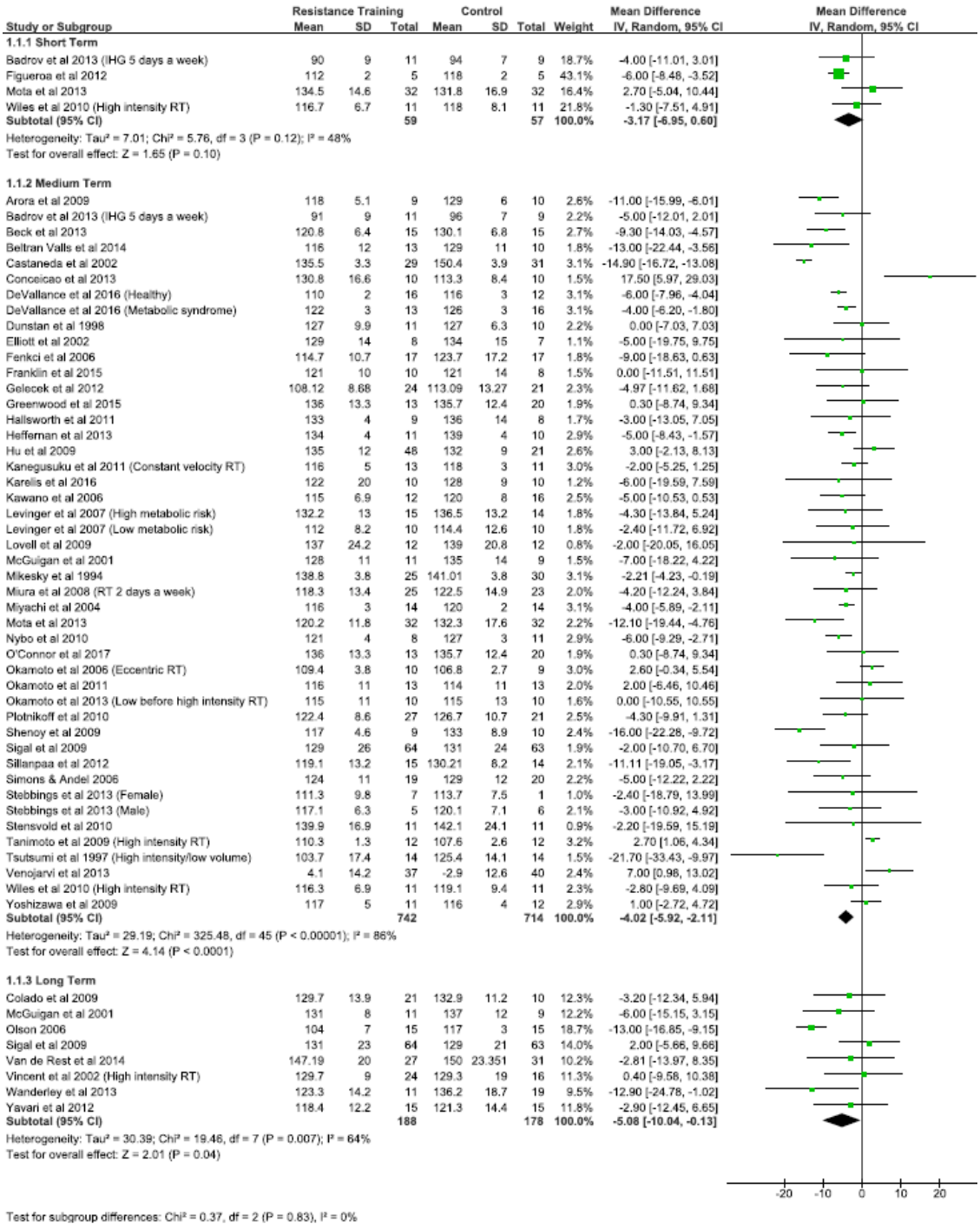


Fig 14. Short-, medium-, long-term effects of resistance exercise training on systolic blood pressure as standardised mean difference and 95% CI.

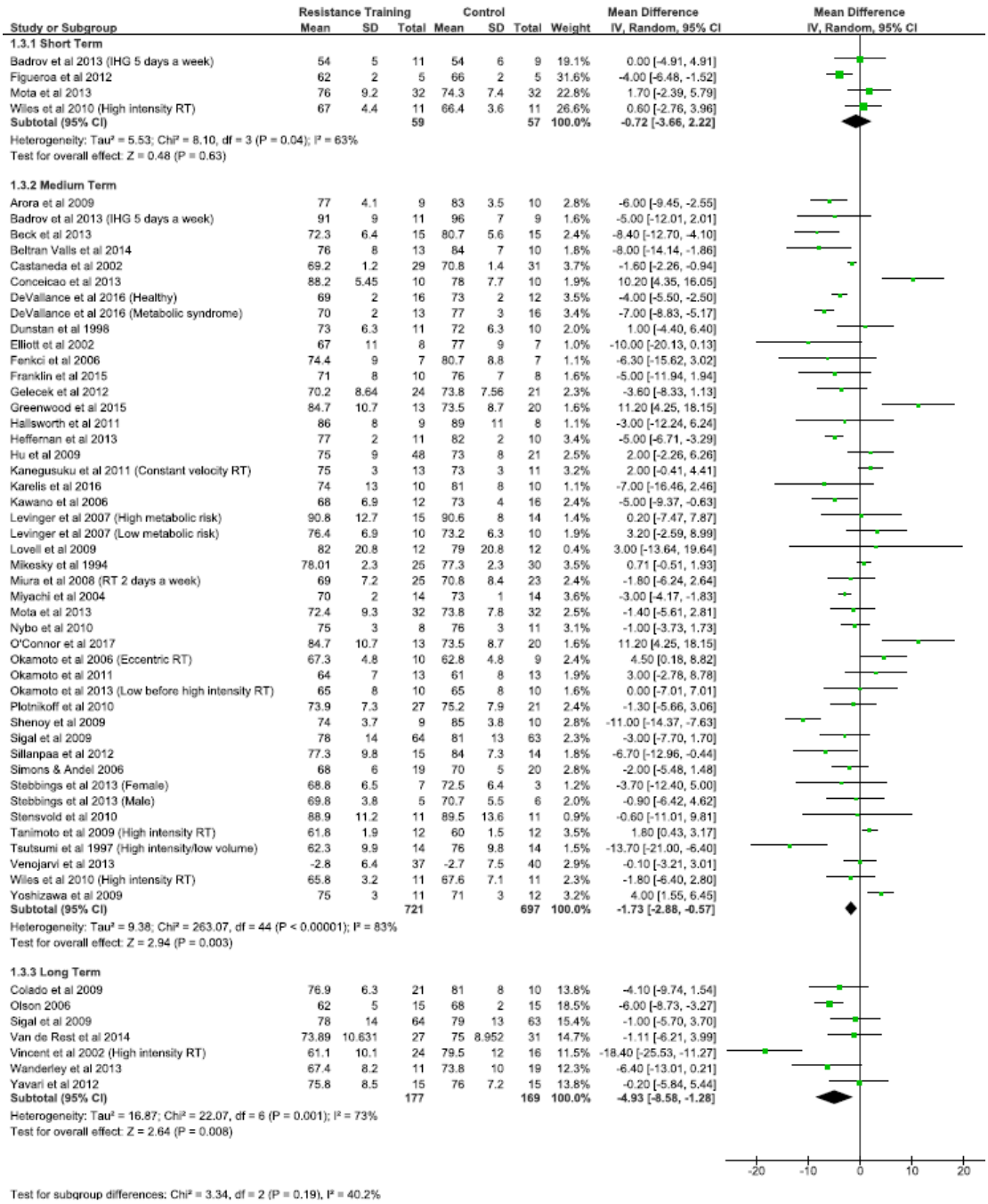


Fig 15. Short-, medium-, long-term effects of resistance exercise training on diastolic blood pressure as standardised mean difference and 95% CI.

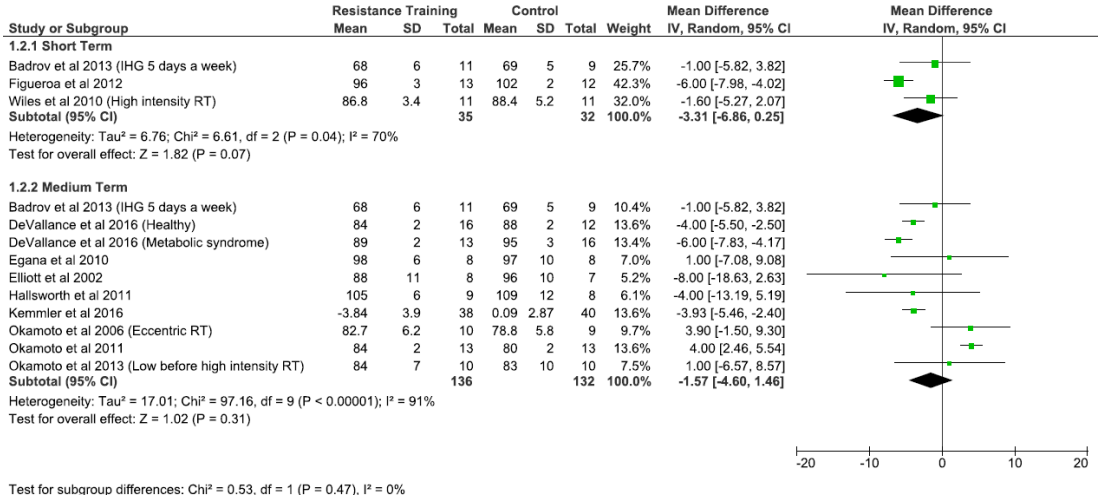


Fig 16. Short- and medium-term effects of resistance exercise training on mean arterial pressure as standardised mean difference and 95% CI.

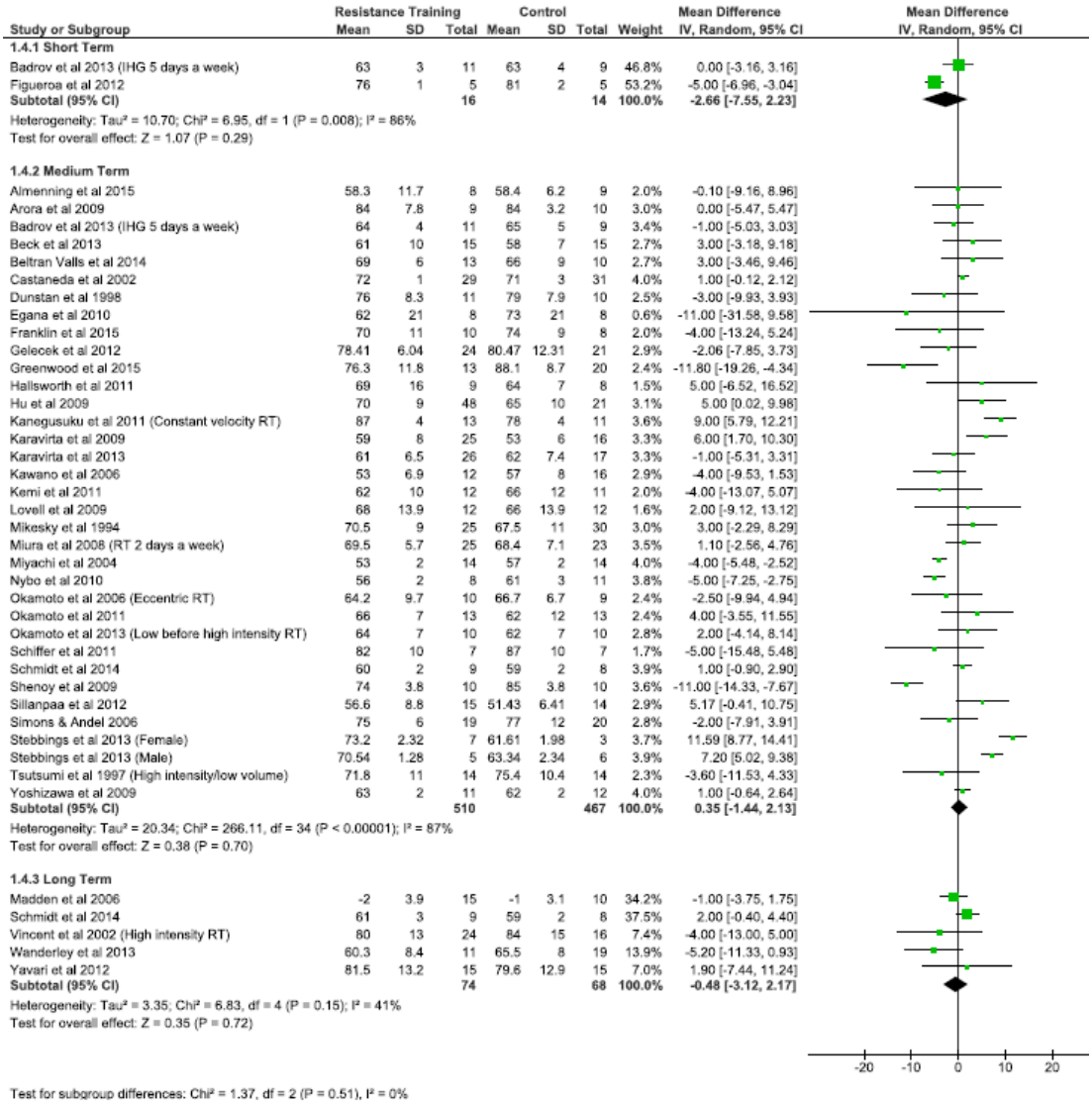


Fig 17. Short-, medium-, long-term effects of resistance exercise training on resting heart rate as standardised mean difference and 95% CI.

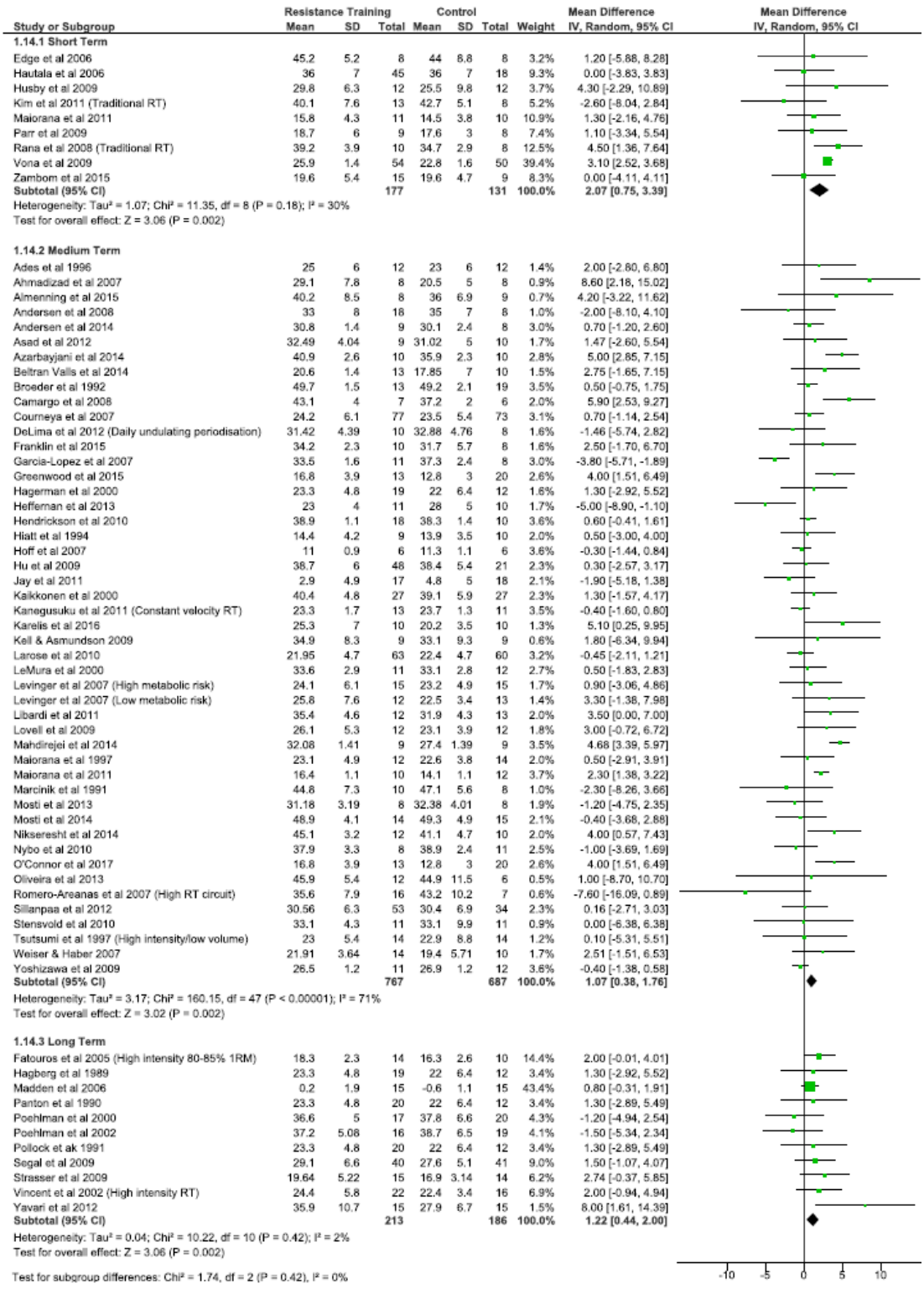


Fig 18. Short-, medium-, long-term effects of resistance exercise training on $\dot{V}O_2$max as standardised mean difference and 95% CI.

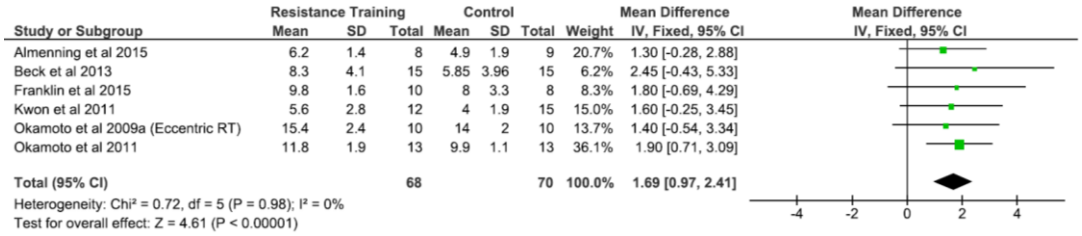


Fig 19. The effects of resistance exercise training on flow mediated dilatation as standardised mean difference and 95% CI.

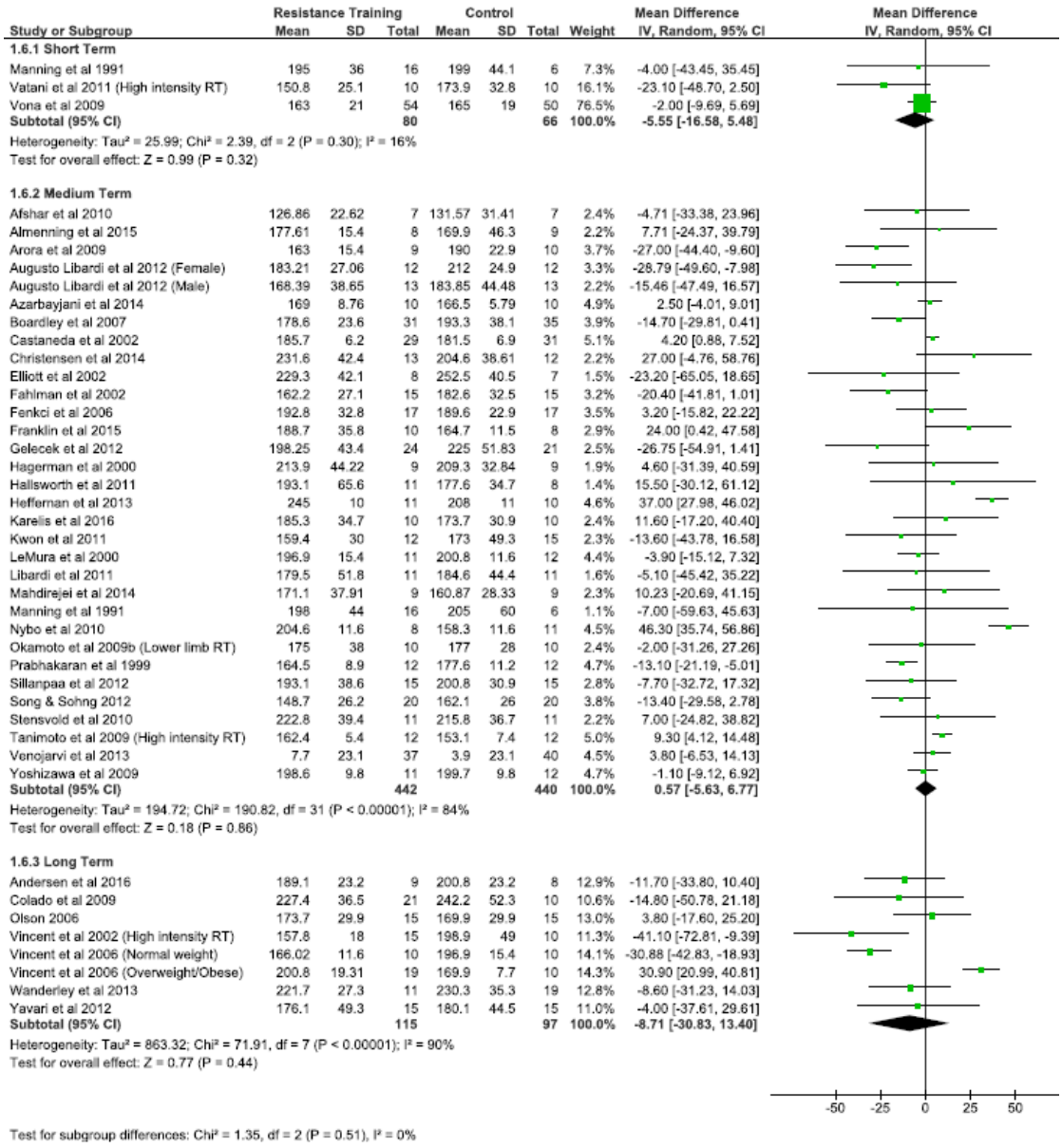


Fig 20. Short-, medium-, long-term effects of resistance exercise training on total cholesterol levels as standardised mean difference and 95% CI.

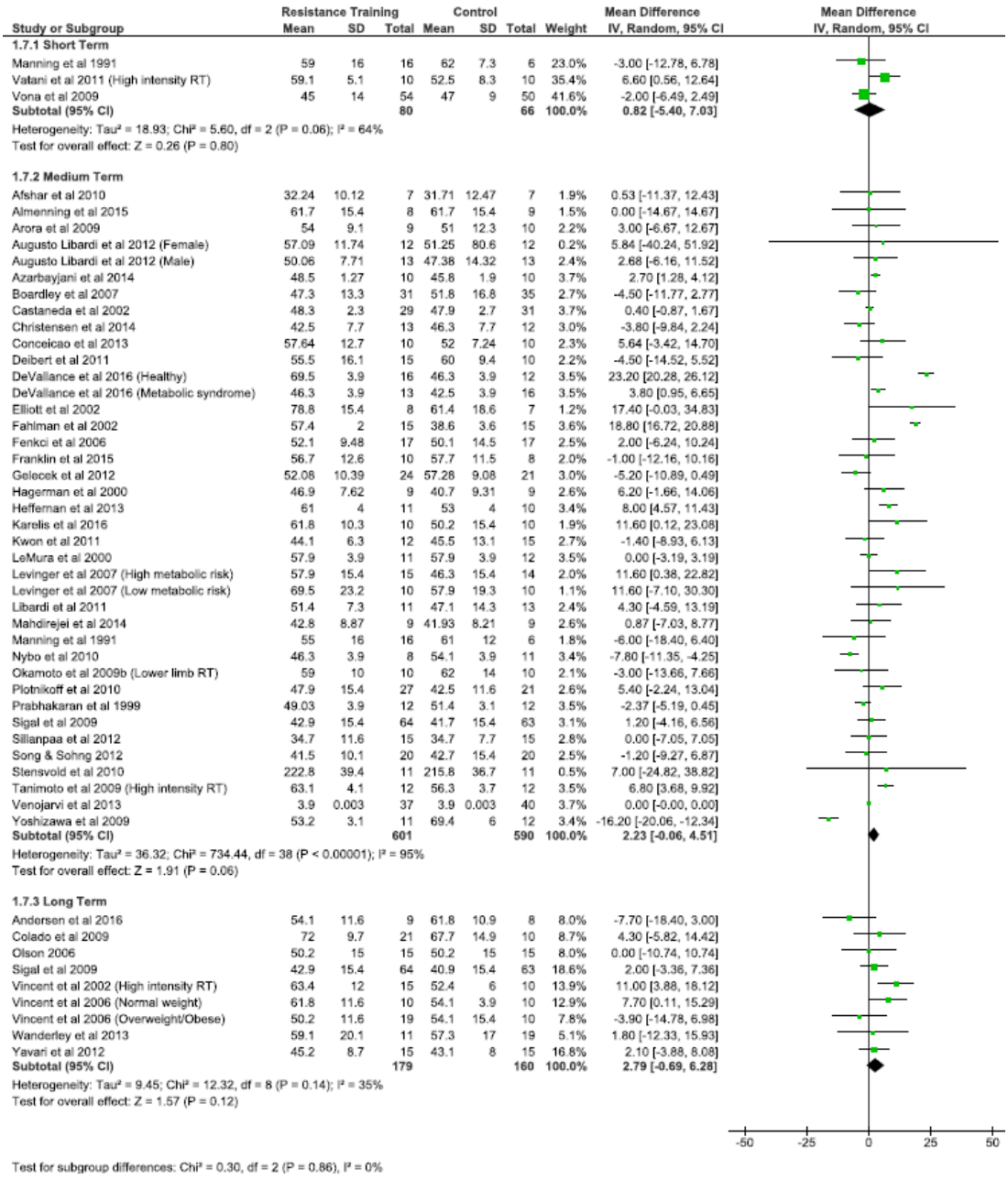


Fig 21. Short-, medium-, long-term effects of resistance exercise training on high density lipoprotein cholesterol levels as standardised mean difference and 95% CI.

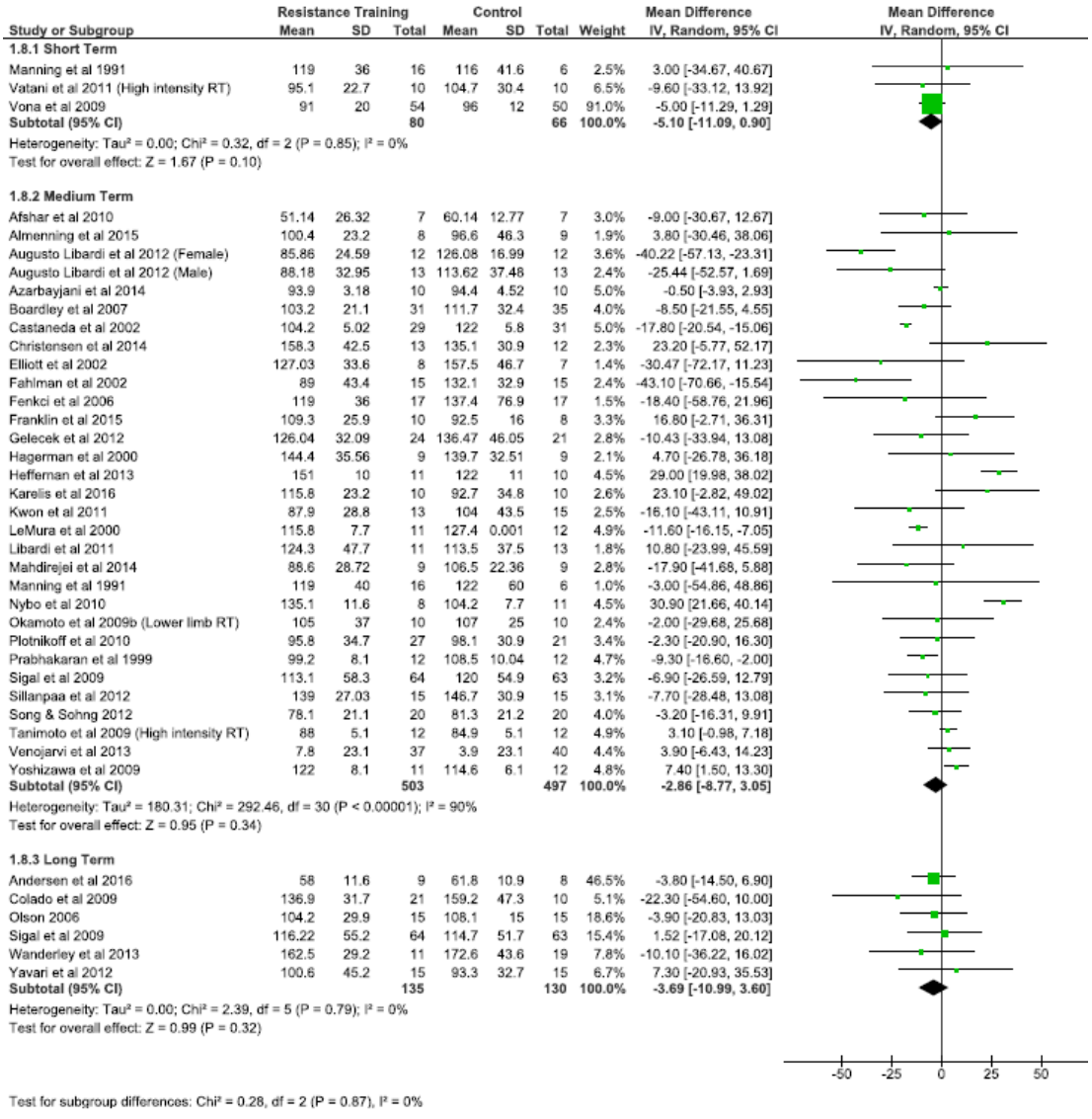


Fig 22. Short-, medium-, long-term effects of resistance exercise training on low density lipoprotein cholesterol levels as standardised mean difference and 95% CI.

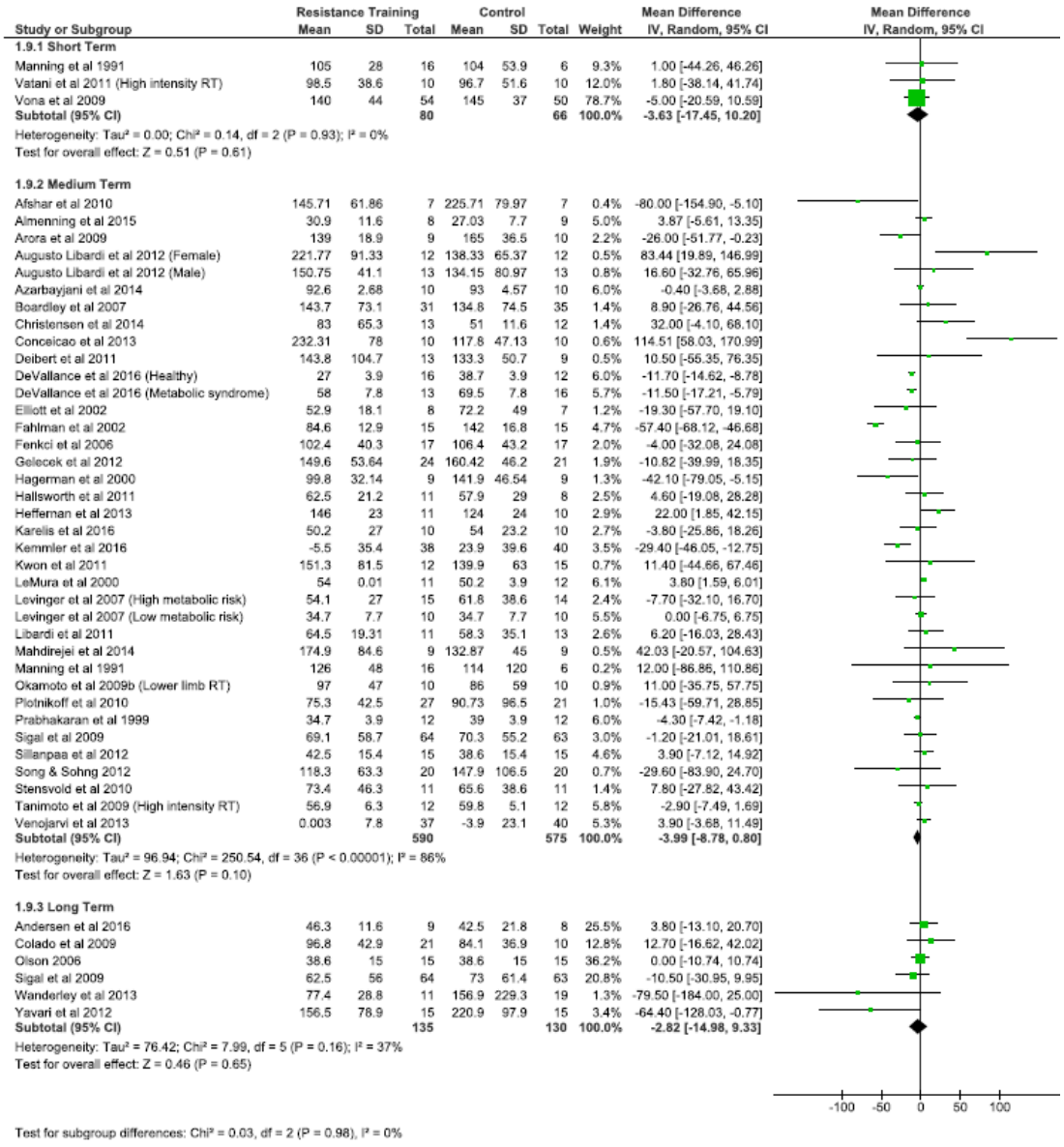


Fig 23. Short-, medium-, long-term effects of resistance exercise training on triglyceride levels as standardised mean difference and 95% CI.

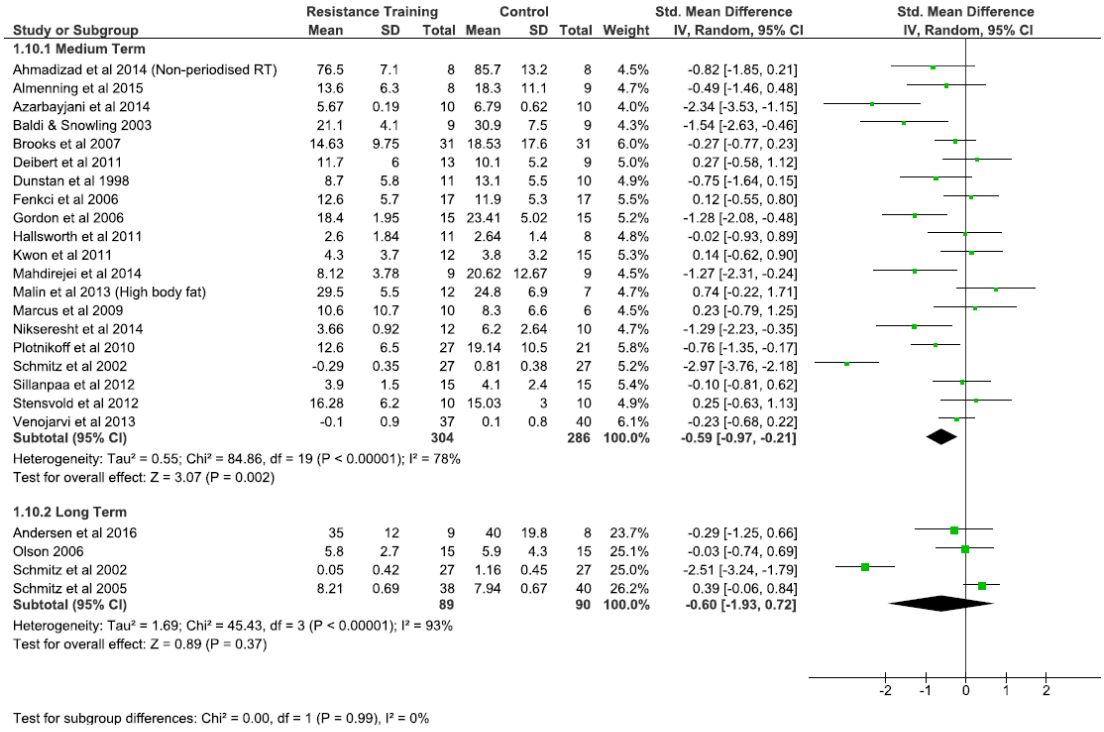


Fig 24. Medium- and long-term effects of resistance exercise training on fasted insulin levels as standardised mean difference and 95% CI.

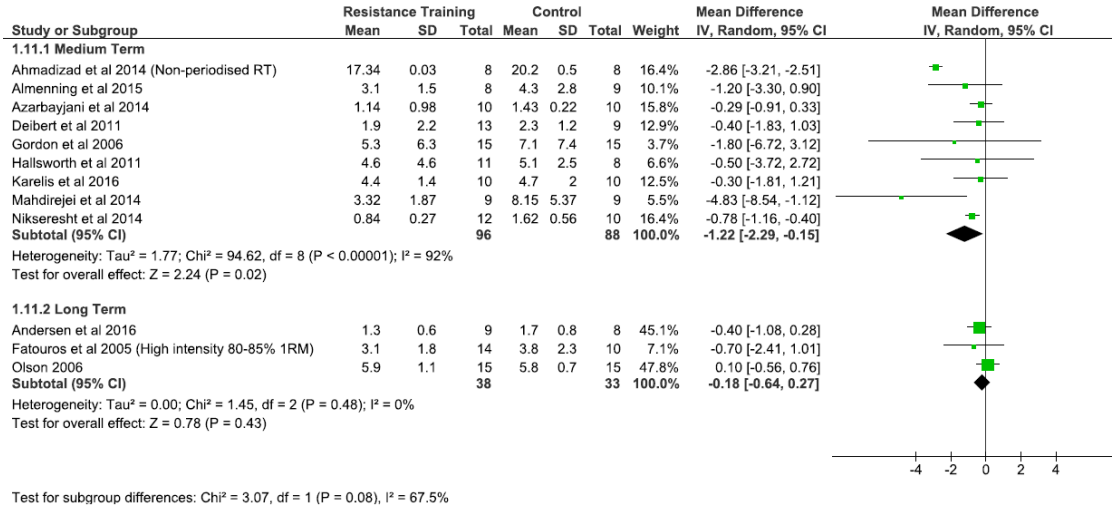


Fig 25. Medium- and long-term effects of resistance exercise training on insulin resistance (HOMA-IR) as standardised mean difference and 95% CI.

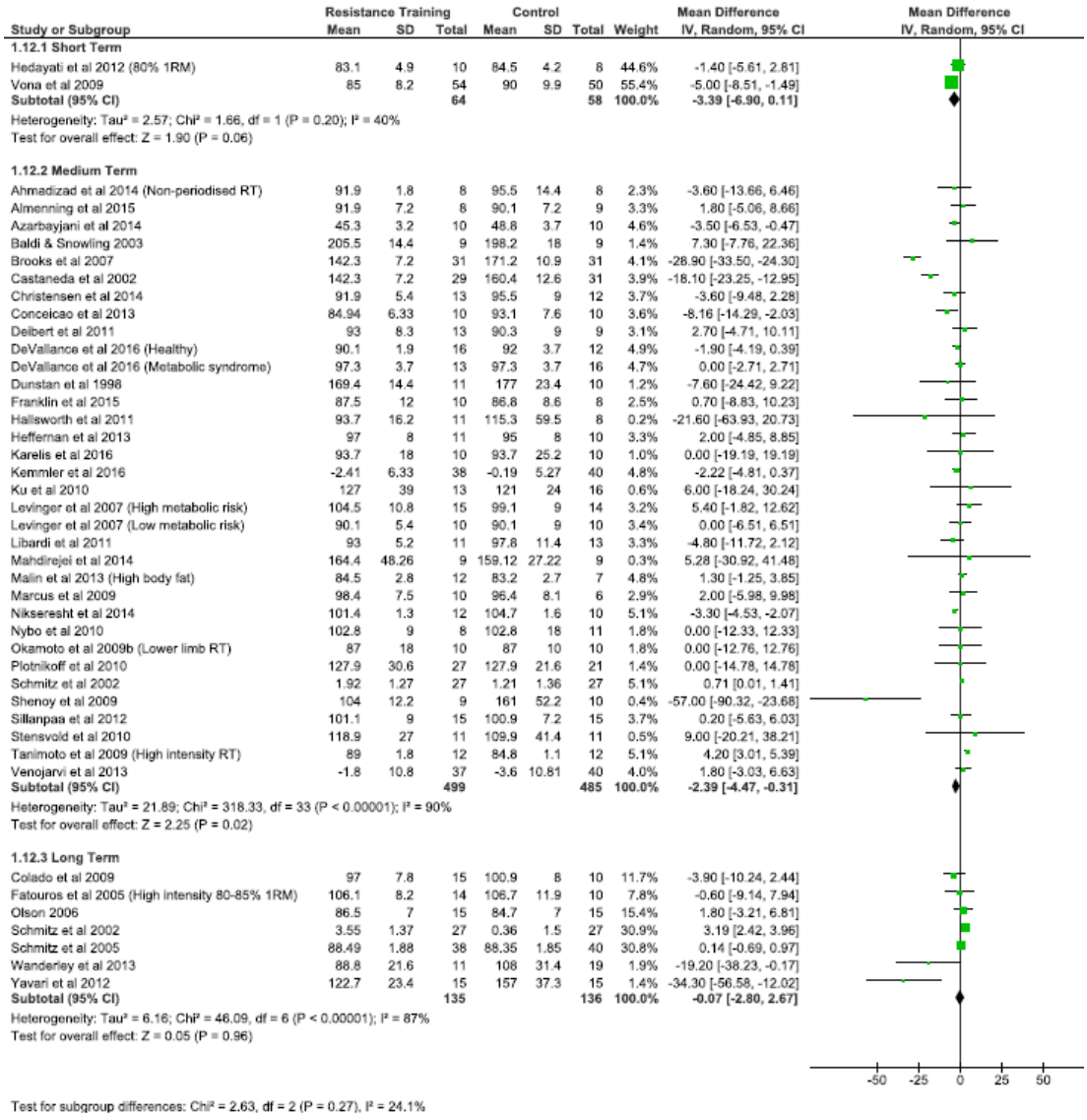


Fig 26. Short-, medium-, long-term effects of resistance exercise training on fasted glucose levels as standardised mean difference and 95% CI.

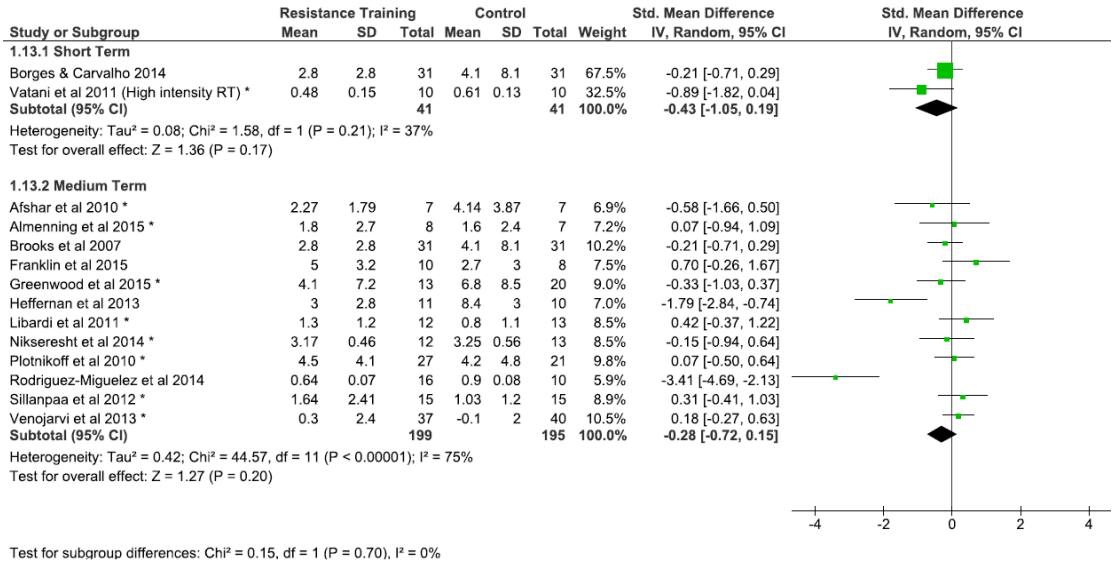


Fig 27. Short- and medium-term effects of resistance exercise training on c-reactive protein levels as standardised mean difference and 95% CI.

Table 1. The short- (ST), medium- (MT) and long-term (LT) effects of RET on all outcomes reported in healthy young adults aged 18-40 years.

Blood marker		Number of studies	Number of participants		Mean difference [95% CI]	P values	Heterogeneity
			RT	CON			
SBP (mmHg)	*MT*	11	150	122	-0.56 [-1.57, 0.44] †	0.27	χ^2 = 49.4, I^2 = 80%, P < 0.00001
DBP (mmHg)	*MT*	11	150	124	-0.81 [-1.59, -0.04] †	0.04*	χ^2 = 41.91, I^2 = 76%, P < 0.00001
MAP (mmHg)	*MT*	4	44	41	3.48 [2.09, 4.87]	< 0.00001*	χ^2 = 4.19, I^2 = 28%, P = 0.24
RHR (bpm)	*MT*	12	157	130	0.12 [-0.79, 1.03]	0.79	χ^2 = 163.07, I^2 = 93%, P < 0.00001
V̇O2max (ml/kg/min)	*ST*	3	31	24	2.53 [-0.01, 5.07] †	0.05*	χ^2 = 5.06, I^2 = 61%, P = 0.08
	MT	11	161	126	0.91 [0.29, 1.53] †	0.004*	χ^2 = 28.23, I^2 = 65%, P = 0.002
	LT	2	33	39	-1.35 [-4.03, 1.33]	0.32	χ^2 = 0.01, I^2 = 0%, P = 0.91
Total Cholesterol (mg/dL)	*MT*	6	63	67	6.23 [2.97, 9.49]	0.0002*	χ^2 = 83.22, I^2 = 94%, P < 0.00001
HDL-chol (mg/dL)	*MT*	6	78	76	1.85 [0.74, 2.97] †	0.001*	χ^2 = 42.3, I^2 = 88%, P < 0.00001
LDL-chol (mg/dL)	*MT*	6	78	76	-0.30 [-2.49, 1.88] †	0.78	χ^2 = 70.26, I^2 = 93%, P < 0.00001
Triglycerides (mg/dL)	*MT*	5	70	65	1.74 [0.04, 3.44]	0.04*	χ^2 = 9.64, I^2 = 59%, P = 0.05
Fasted glucose (mg/dL)	*MT*	4	40	43	3.12 [2.02, 4.22]	< 0.00001*	χ^2 = 21.93, I^2 = 86%, P < 0.0001

* Indicates statistical significance. † Indicates favouring resistance exercise training. ST – short term, MT – medium term, LT – long term, SBP – systolic blood pressure, DBP - diastolic blood pressure, MAP – mean arterial pressure, RHR – resting heart rate, $\dot{V}O_2$max – aerobic capacity, HDL-chol – high density lipoprotein cholesterol, LDL-chol – low density lipoprotein cholesterol.

Table 2. The short- (ST), medium- (MT) and long-term (LT) effects of RET on all outcomes reported in healthy older adults ≥ 41 years of age.

Blood marker		Number of studies	Number of participants		Mean difference [95% CI]	P values	Heterogeneity
			RT	CON			
SBP (mmHg)	*MT*	12	180	166	-4.36 [-5.73, -2.99] †	< 0.00001*	χ^2 = 41.02, I^2 = 73%, P < 0.00001
	LT	3	72	57	-1.89 [-7.66, 3.88] †	0.52	χ^2 = 0.31, I^2 = 0%, P = 0.86
DBP (mmHg)	*MT*	12	180	166	-1.51 [-2.47, -0.54] †	0.002*	χ^2 = 75.02, I^2 = 85%, P < 0.00001
	LT	3	72	57	-5.95 [-9.30, -2.61] †	0.0005*	χ^2 = 15.57, I^2 = 87%, P = 0.0004
MAP (mmHg)	*MT*	3	32	27	-3.91 [-5.37, -2.45] †	< 0.00001*	χ^2 = 2.0, I^2 = 0%, P = 0.37
RHR (bpm)	*MT*	13	214	186	1.80 [0.84, 2.77]	0.0003*	χ^2 = 34.42, I^2 = 65%, P = 0.0006
	LT	3	48	34	0.52 [-1.25, 2.30]	0.56	χ^2 = 3.6, I^2 = 44%, P = 0.17
V̇O2max (ml/kg/min)	*MT*	13	220	186	-0.31 [-0.90, 0.27]	0.3	χ^2 = 29.33, I^2 = 59%, P = 0.004
	LT	7	125	91	1.30 [0.47, 2.13] †	0.002*	χ^2 = 2.28, I^2 = 0%, P = 0.002
Total Cholesterol (mg/dL)	*MT*	8	109	106	-8.20 [-14.52, -1.89] †	0.01*	χ^2 = 10.4, I^2 = 33%, P = 0.17
	LT	3	45	28	-19.99 [-36.18, -3.80] †	0.02*	χ^2 = 2.32, I^2 = 14%, P = 0.31
HDL-chol (mg/dL)	*MT*	11	150	140	11.55 [10.16, 12.94] †	< 0.00001*	χ^2 = 368.51, I^2 = 97%, P < 0.00001
	LT	3	45	28	5.01 [-0.10, 10.13] †	0.05	χ^2 = 8.16, I^2 = 75%, P = 0.02
LDL-chol (mg/dL)	*MT*	8	109	108	-1.60 [-6.58, 3.37] †	0.53	χ^2 = 43.85, I^2 = 84%, P < 0.00001
	LT	2	30	18	-5.63 [-15.79, 4.53] †	0.28	χ^2 = 1.14, I^2 = 12%, P = 0.29
Triglycerides (mg/dL)	*MT*	10	151	146	-13.27 [-15.92, -10.61] †	< 0.00001*	χ^2 = 112.64, I^2 = 92%, P < 0.00001
	LT	2	30	18	6.02 [-8.62, 20.66]	0.42	χ^2 = 0.27, I^2 = 0%, P = 0.61
Fasted insulin (µU/ml)	*MT*	3	73	73	-1.09 [-1.28, -0.89] †	< 0.00001*	χ^2 = 2.1, I^2 = 5%, P = 0.35
	LT	2	47	48	0.27 [-0.03, 0.57]	0.08	χ^2 = 0.43, I^2 = 0%, P = 0.51
HOMA-IR	*LT*	2	23	18	-0.44 [-1.07, 0.19] †	0.17	χ^2 = 0.1, I^2 = 0%, P = 0.75
Fasted glucose (mg/dL)	*MT*	7	134	130	-4.82 [-6.26, -3.38] †	< 0.00001*	χ^2 = 123.38, I^2 = 95%, P < 0.00001
	LT	3	56	47	3.06 [2.30, 3.82]	< 0.00001*	χ^2 = 5.45, I^2 = 63%, P = 0.07
CRP (mg/L)	*MT*	4	74	69	-0.26 [-0.32, -0.20] †	< 0.00001*	χ^2 = 4.71, I^2 = 36%, P = 0.19

* Indicates statistical significance. † Indicates favouring resistance exercise training. ST – short term, MT – medium term, LT – long term, HDL-chol – high density lipoprotein cholesterol, LDL-chol – low density lipoprotein cholesterol, HOMA-IR – insulin resistance, CRP – C-reactive protein.

Table 3. The short- (ST), medium- (MT) and long-term (LT) effects of RET on all outcomes reported in older adults ≥ 41 years old with cardiometabolic risk factors

Blood marker		Number of studies	Number of participants		Mean difference [95% CI]	P values	Heterogeneity
			RT	CON			
SBP (mmHg)	*ST*	2	37	37	-5.19 [-7.55, -2.83] †	< 0.0001*	$\chi^2 = 4.4$, $I^2 = 77\%$, P = 0.04
	MT	17	304	312	-8.80 [-9.90, -7.69] †	< 0.00001*	$\chi^2 = 95.83$, $I^2 = 83\%$, P < 0.00001
	LT	4	101	106	-3.42 [-8.03, 1.19] †	0.15	$\chi^2 = 4.69$, $I^2 = 36\%$, P = 0.2
DBP (mmHg)	*ST*	2	37	37	-2.47 [-4.59, -0.35] †	0.02*	$\chi^2 = 5.45$, $I^2 = 82\%$, P = 0.02
	MT	15	219	230	-2.55 [-3.09, -2.01] †	< 0.00001*	$\chi^2 = 103.88$, $I^2 = 87\%$, P < 0.00001
	LT	3	90	97	-1.99 [-5.15, 1.18] †	0.22	$\chi^2 = 2.27$, $I^2 = 12\%$, P = 0.32
MAP (mmHg)	*MT*	2	22	24	-5.92 [-7.72, -4.13] †	< 0.00001*	$\chi^2 = 0.17$, $I^2 = 0\%$, P = 0.68
RHR (bpm)	*MT*	6	81	89	-0.44 [-1.45, 0.58] †	0.4	$\chi^2 = 55.3$, $I^2 = 91\%$, P < 0.00001
	LT	2	26	34	-3.06 [-8.19, 2.06] †	0.24	$\chi^2 = 1.55$, $I^2 = 36\%$, P = 0.21
$\dot{V}O_2$Peak (ml/kg/min)	*ST*	3	74	68	3.02 [2.45, 3.59] †	< 0.00001*	$\chi^2 = 1.74$, $I^2 = 0\%$, P = 0.42
	MT	11	178	186	2.38 [1.78, 2.98] †	< 0.00001*	$\chi^2 = 47.0$, $I^2 = 79\%$, P < 0.00001
Total Cholesterol (mg/dL)	*MT*	10	125	127	6.65 [3.70, 9.60]	< 0.00001*	$\chi^2 = 62.61$, $I^2 = 86\%$, P < 0.00001
	LT	2	26	34	-7.16 [-25.94, 11.61] †	0.45	$\chi^2 = 0.05$, $I^2 = 0\%$, P = 0.82
HDL-chol (mg/dL)	*MT*	14	243	243	1.86 [0.85, 2.87] †	0.0003*	$\chi^2 = 26.2$, $I^2 = 50\%$, P = 0.02
	LT	3	90	97	2.03 [-1.81, 5.87] †	0.3	$\chi^2 = 0.0$, $I^2 = 0\%$, P = 1.0
LDL-chol (mg/dL)	*MT*	9	186	182	-13.42 [-15.94, -10.91] †	< 0.00001*	$\chi^2 = 98.19$, $I^2 = 92\%$, P < 0.00001
	LT	3	90	97	-0.22 [-13.57, 13.13] †	0.97	$\chi^2 = 0.86$, $I^2 = 0\%$, P = 0.65
Triglycerides (mg/dL)	*MT*	14	225	220	-5.75 [-9.62, -1.87] †	0.004*	$\chi^2 = 28.15$, $I^2 = 54\%$, P = 0.009
	LT	3	90	97	-17.69 [-36.83, 1.45] †	0.07	$\chi^2 = 3.89$, $I^2 = 49\%$, P = 0.14
Fasted insulin (µU/ml)	*MT*	11	139	128	-1.44 [-2.43, -0.45] †	0.004*	$\chi^2 = 38.07$, $I^2 = 74\%$, P < 0.0001
HOMA-IR	*MT*	4	43	40	-2.84 [-3.19, -2.50] †	< 0.00001*	$\chi^2 = 3.31$, $I^2 = 9\%$, P = 0.35
Fasted glucose (mg/dL)	*MT*	14	187	180	-2.19 [-4.09, -0.29] †	0.02*	$\chi^2 = 59.26$, $I^2 = 78\%$, P < 0.00001
	LT	2	26	34	-25.57 [-40.04, -11.10] †	0.0005*	$\chi^2 = 1.02$, $I^2 = 2\%$, P = 0.0005
CRP (mg/L)	*MT*	4	58	58	-2.47 [-3.97, -0.98] †	0.001*	$\chi^2 = 9.93$, $I^2 = 70\%$, P = 0.02

* Indicates statistical significance. † Indicates favouring resistance exercise training. ST – short term, MT – medium term, LT – long term, HDL-chol – high density lipoprotein cholesterol, LDL-chol – low density lipoprotein cholesterol, HOMA-IR – insulin resistance, CRP – C-reactive protein.

Appendix 3a. *Development Session Discussion Schedule*

Session 1

Part 1 – Discussion

- Introduce self and project
- Each individual introduce themselves
- Definitions
    - Physical activity - Physical activities are activities that get your body moving such as gardening, walking the dog and taking the stairs instead of the lift.
    - Exercise - Exercise is a form of physical activity that is planned, structured, and repetitive such as weight training, tai chi, or an aerobics class.
- Bearing in mind the definitions I have given you , do you exercise regularly?
    - How do you exercise?
        - General activities of daily living
        - Aerobic
        - Resistance
        - Gym member
- Can you tell me the differences between aerobic and resistance exercise?
    - How do you think each of these could benefit your health?
    - Can you tell me your opinions on resistance exercise in general?
    - If I told you that resistance exercise could bring about more beneficial effects to health and help alleviate some of the side effects of your treatment, does this change your opinion of it?

Part 2 – Exercises

Patients will be given a range of exercises to try under the instruction of the researcher.

Part 3 – Feedback

- Were there any exercises that you particularly liked?
- Were there any exercises that you particularly disliked?
- How did you find using the resistance bands?
- Were the instructions on each exercise clear enough?
    - Could they be improved? If so, how?
- If you were to be given a programme comprised of the exercises that you've tried today would you be happy with it?

    - Are there any other exercises that you would like to see in a programme?
    - Do you think these exercises would work well in your home?

Session2

Part 1 – Discussion

- Introduce self and project
- Each individual introduce themselves
- Do you exercise regularly?
    - How do you exercise?
        - General activities of daily living
        - Aerobic
        - Resistance
        - Gym member
- Do you want to increase your exercise levels?
    - If not, why not?
    - What do you think would help you reach your desired level of exercise?
- Do you think that exercise could benefit your recovery or help alleviate some of the side-effects of your treatment?
    - If so, how?
- Were you given any exercise advice upon diagnosis or after your treatment?
    - If you were given advice, did you do what they advised? If not, why not?
    - If not, would you have liked some exercise advice?

Part 2 – Exercises

Patients will be given an exercise instruction manual and taken through the whole exercise programme by the researcher. Patients will wear a heart rate monitor and watch, have blood pressure taken after some of the exercises and provide ratings of perceived exertion.

Medical professional present.

Part 3 – Feedback

- First of all can I get your feedback on the manual you were given?
    - Anything you would change?
    - Anything you would add in/remove?

    - Anything that you think is particularly useful in there?
- Please could you give me some general feedback about the programme?
    - Do you feel like it worked your whole body?
    - Do you like the mix of body weight and resistance band exercises?
    - Were there any exercises that you particularly liked?
    - Were there any exercises that you particularly disliked?
    - Is there anything extra that you would add in?
    - Do you think it would be easy to complete within your home?
- Is this something you would have been interested in doing had you been offered it upon diagnosis?
    - Why?
    - What benefits do you think you can get from this programme?
- How would you feel if I asked you to complete this programme at least twice a week for 12 weeks?
    - Would you stick to it?
    - Is there anything that I could do to help you stick to it?
- So if I now told you that you would have two sessions a week supervised by myself for the first two weeks, the second two weeks you would complete one session with me and one at home and then for the next 8 weeks you would complete all sessions at home but have regular contact with myself via text/email, how would you feel?

Appendix 3b. *Exercise Manual*

EXERCISE DIARY & MANUAL

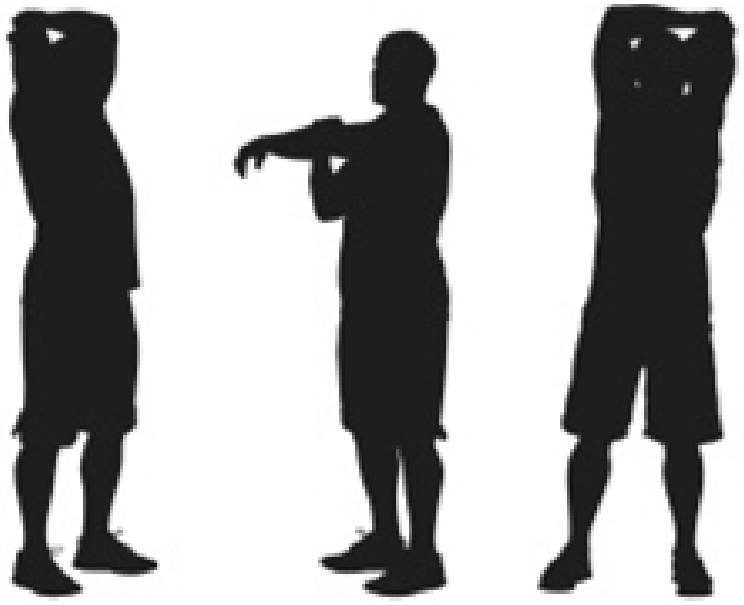


Table of Contents

Why should you be more active?

Physical health benefits of an active lifestyle:

- Improve mobility and independence
- Feel stronger
- More energetic
- Improve bone density and flexibility
- Help maintain a healthy body weight
- Reduce cancer-related fatigue

Mental health benefits of an active lifestyle:

- Improve sleep quality
- Reduce stress and anxiety levels
- Boost your self esteem
- Increase confidence and mood
- Improve overall mental health

Social health benefits of an active lifestyle:

- Increase social integration
- Meet new people and create new friendships
- Time to relax and have fun

How much physical activity is needed for health?

The Department of Health recommends:

- At least 2½ hours of moderate intensity activity in bouts of 10 minutes or more a week

OR

- 1¼ hours of vigorous intensity activity spread across the week

OR

- Combinations of both moderate and vigorous intensity activity
- Adults should also undertake muscle strengthening exercises on at least two days a week
- Minimise the amount of time spent being sedentary (sitting) for extended periods



Here are some great websites that provide lots of exercise advice and give links to local opportunities to help you get started:

NHS Choices: http://www.nhs.uk/pages/home.aspx

Change4Life Local Activities: http://www.nhs.uk/change4life/Pages/local-change-for-life-activities.aspx

Macmillan Cancer Support Activities Near You: http://www.macmillan.org.uk/information-and-support/coping/maintaining-a-healthy-lifestyle/keeping-active/activities-near-you.html

What is moderate and vigorous intensity exercise?

Moderate intensity physical activity refers to an activity that increases your heart rate to an intensity equivalent to brisk walking or steady cycling but you do not break into a sweat. You are just about able to maintain a conversation.

Examples:

- Mowing the lawn
- Hoovering
- Cycling 10-12mph
- Golf – walking/pulling clubs
- Carrying/moving moderate loads (< 20kg)

Vigorous intensity physical activity produces a large increase in breathing and heart rate to an intensity equivalent to jogging or cycling uphill. You won't be able to say more than a few words without pausing for a breath.

Examples:

- Cycling 12-14mph
- Running
- Competitive sports and games (e.g. football, volleyball, hockey)
- Carrying/moving heavy loads (> 20kg)
- Heavy shovelling/digging

How can I build muscular strength?

You can build muscular strength by…

- Lifting weights

- Exercising with resistance bands

- Doing exercises that use your body weight (e.g. press ups)

- It is important that you work all major muscle groups – the legs, back, abdomen, chest, shoulders and arms

- As exercise becomes easier, increase the weight/resistance or do an extra set!

Exercise after Prostate Cancer

Prostate cancer is the most common form of male cancer in the United Kingdom. In recent years there have been marked improvements in early detection and innovations in treatment of prostate cancer. Currently treatment options are dependent on tumour characteristics (type, size, Gleasongrade, Prostate Specific Antigen (PSA; evidence of spread of disease) and patient characteristics and importantly preferences (including general health).

Studies have provided convincing evidence that exercise reduces cancer-related fatigue, strengthens immune function and improves quality of life in prostate cancer patients who have undergone various treatments. Aerobic exercise (e.g. jogging and cycling) is reported to improve peak oxygen uptake, decrease fatigue and prevent a decline in physical function during treatment. Resistance exercise (e.g. lifting weights and using resistance bands) are also effective in reducing cancer-related fatigue but may bring about more beneficial effects compared to aerobic training in relation to muscle strength, quality of life and well-being, as well as reductions in blood pressure and waist circumference after prostate cancer treatments.

Exercise Tips…

- Wear comfortable clothing and suitable shoes (e.g. trainers)
- Exercise at a time that suits you
- Don’t exercise on an empty stomach but also leave about 2 hours after eating a large meal before exercising
- Stay well hydrated

Your home exercise plan

- Remember to warm up with gentle stretching to help prevent injury and help increase:
    - Blood flow to muscles
    - Heart rate
    - Oxygen and nutrient supply to muscles

- Use different bands for different exercises if necessary
- Mix up the order in which you do the exercises
- Remember to cool down. Gentle exercise and static stretching (hold for 10 seconds) helps to:
    - Return the body to its pre-exercise state
    - Reduce the heart rate gradually

- Don’t exercise if you are injured or ill

Your bands…

	Yellow	Red	Green	Blue	Black
Resistance Level	Thin	Medium	Heavy	Extra Heavy	Special Heavy
Weight at 100% elongation	1.3kgs	1.8kgs	2.3kgs	3.2kgs	4.4kgs

How can I make progress?

1. **Make it fun and personalise it!**

   Try exercising with music and doing your exercises both inside and outside the house. You are more likely to keep it up if you enjoy it!

2. **Track your progress**

   Keep a daily record in your exercise diary and reflect on the progress you make, this can help keep you motivated too. Set yourself some goals too – you can do this on the next page!

3. **Involve family and friends**

   Exercising on your own can be a dull prospect. Exercising with a friend or family member can push you to work harder and you will have more fun.

4. **Be positive, stay positive!**

   Everyone can feel low, have no motivation or feel tired before and during exercise. Here are some tips to staying positive:

   - Remember sessions you have performed well in or enjoyed the most and try to replicate them
   - Remind yourself of the benefits of exercise
   - Think about you how will feel when you make progress and get fitter
   - Encourage yourself with positive statements, for example “you can do this!” or “take a deep breath and go!”

5. **Discuss any issues you have with us over the phone or via email**

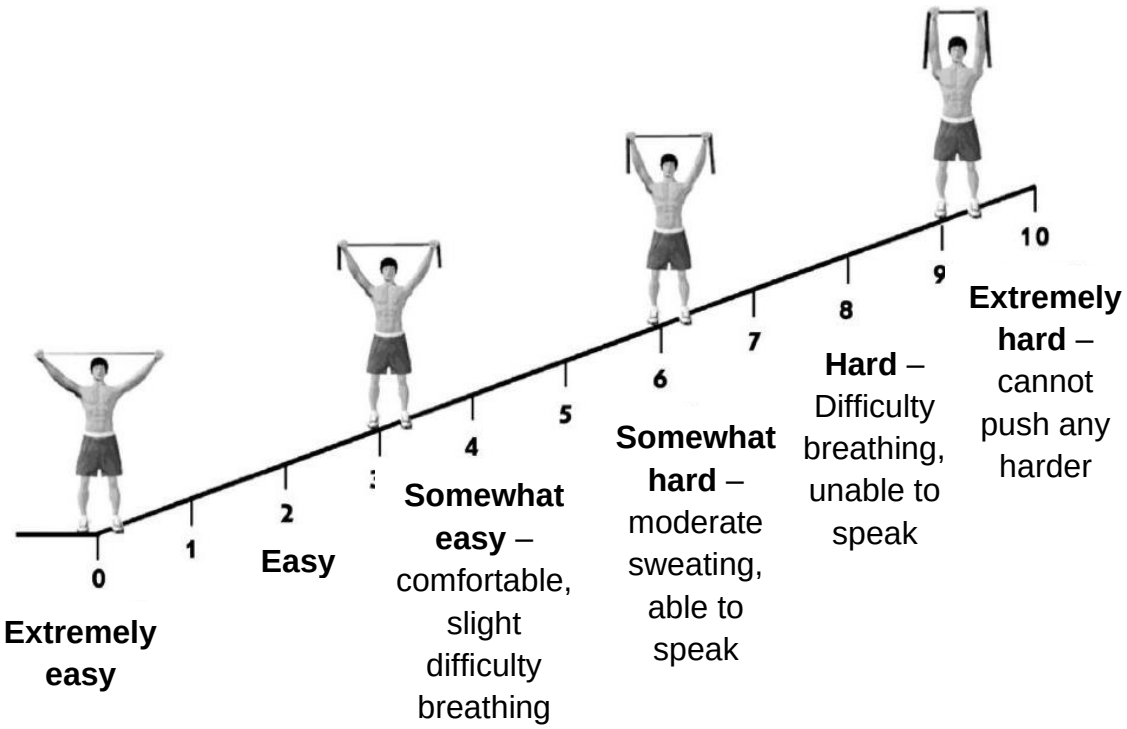
Set yourself some goals

My goal is to…		
SPECIFIC	*What precisely do I want to accomplish?*	
MEASURABLE	*I will measure or track my goal as follows:*	
ATTAINABLE	*Can I achieve this? Do I need to break it down into manageable chunks? How can I break it down?*	
REALISTIC	*Do I have what I need to achieve my goal?*	
TIME	*I will reach my goal by (target date):*	
Obstacles:		**Solutions:**

Resistance Exercise Programme

You need to complete ____ sessions a week made up of ____ sets of ____ reps per exercise.

Please use this scale to rate the intensity of any exercise over the course of the day. You just need to write a number in the box!



Exercise Diary

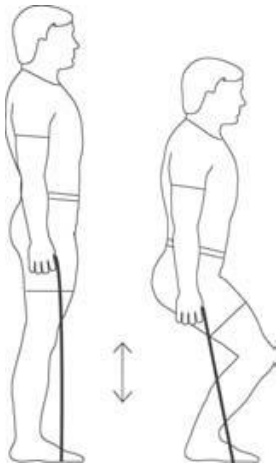
WEEK __ Week commencing: Monday _____

	Exercise	Band	Day	Session Intensity
Session 1				
			Time	
				Notes
			Duration	
Session 2	Exercise	Band	Day	Session Intensity
			Time	
				Notes
			Duration	
Session 3	Exercise	Band	Day	Session Intensity
			Time	
				Notes
			Duration	

Resistance Band Exercises

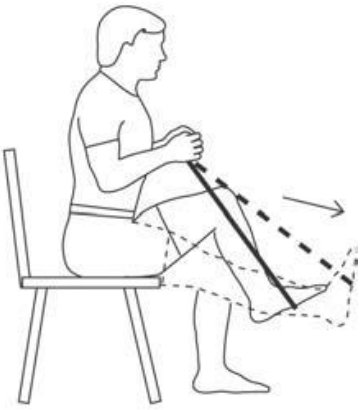
Legs

Squat



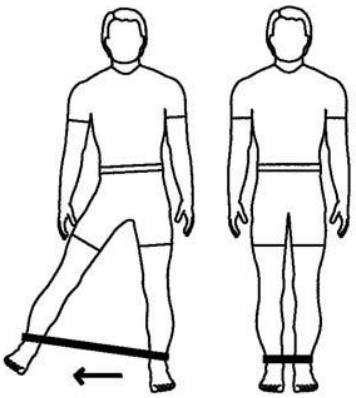
- Place the elastic under feet (more than shoulder width apart), hold ends in hands and keep elbows straight
- Bend knees to 90 degrees
- Straighten knees
- Return to the starting position

Leg Press



- Sit in chair
- Loop elastic around bottom of foot as shown
- Hold elastic in both hands
- Push leg down straightening at knee
- Slowly return to start position and repeat

Quick Kicks

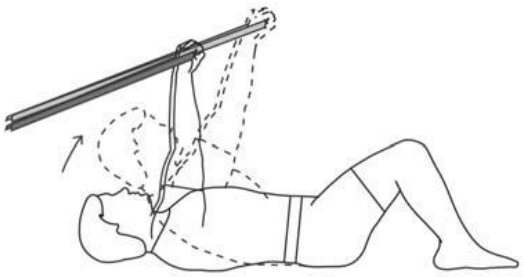


- Knot and loop elastic around ankles
- Kick leg outward and quickly repeat
- Keep toes pointed straight ahead and do not bend trunk

Abdominals

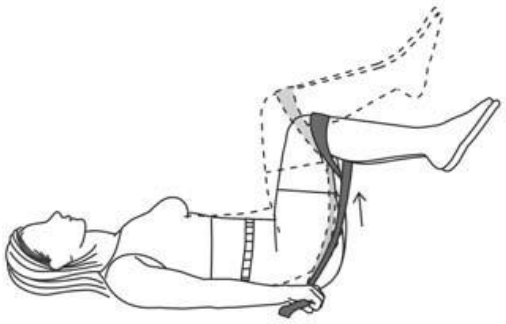
Trunk Curl-up

- Securely attach band to the door anchor near floor
- Lie on back with knees bent, holding ends of bands in hands, arms in front and elbows straight
- Keep hands close together and curl trunk upward, lifting shoulder blades from floor
- Hold and slowly return



Lower Abdominal Crunch

- Lie on back with hips and knees flexed. Stretch band over knees and cross underneath
- Hold each end of band in hands and place arms at sides, with elbows straight
- Lift knees upward, lifting hips off the floor
- Hold and slowly return



Side Bend

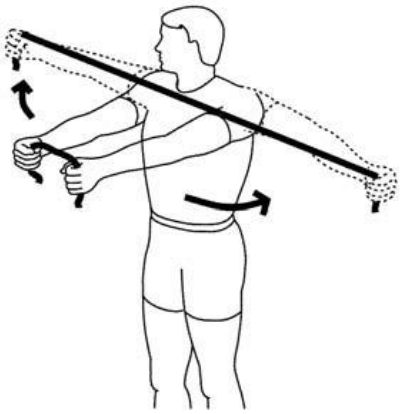
- Stand, holding elastic in right hand, right foot securing other end of elastic as shown
- Bend to left, keeping elbow straight
- Slowly return to start position and repeat
- Repeat sets with other side

Back

Bent Over Row

- Secure elastic under opposite foot
- Hold elastic in involved arm
- Slightly bend hips and knees and support upper body with other arm as shown
- Pull up on elastic, raising elbow to shoulder height
- Slowly return to start position and repeat

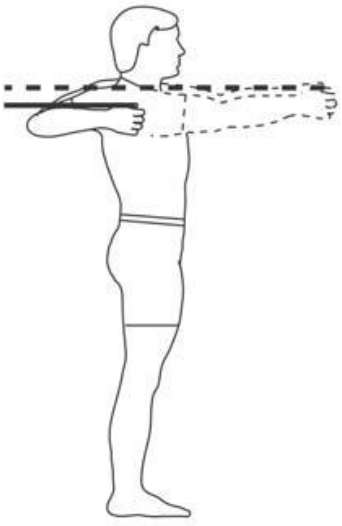
Reverse Flies



- Grasp elastic in hands, elbows straight, as shown
- Move arms away from each other, out to sides
- Slowly return to start position

Chest

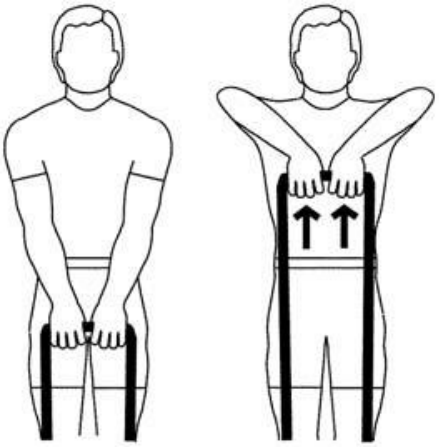
Chest Press



- Attach elastic using the door anchor at shoulder level
- Sit or stand as shown
- Hold elastic in hands, arms out from side, elbows bent, as shown
- Push forward, straightening elbows
- Slowly return to start position and repeat

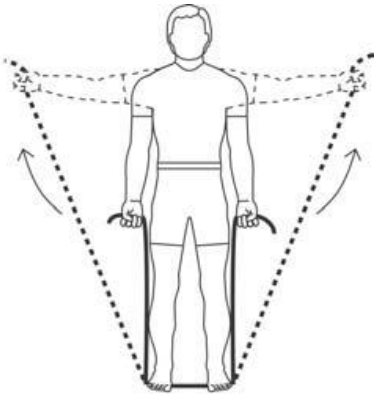
Shoulders

Upright Row



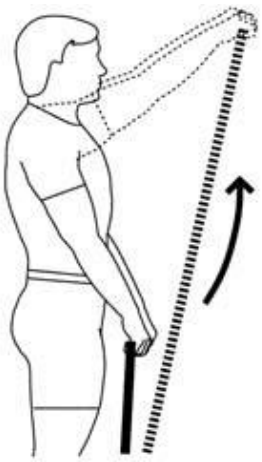
- Stand on elastic
- Grasp elastic in both hands in front of hips, elbows straight
- Lift upward toward chin, bending elbows
- Keep hands close to chest
- Slowly lower and repeat

Lateral Raise



- Stand on elastic and hold elastic in both hands
- Begin with arms at sides with palms facing forward
- Keep elbows straight and lift arms to shoulder level
- Slowly lower and repeat

Front Raise



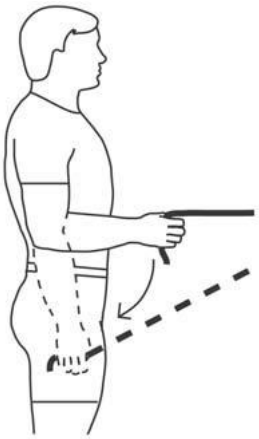
- Stand on the elastic and hold at waist level as shown
- Grasp elastic and pull arm backwards keeping elbow straight
- Slowly return to start position

Arms

Bicep Curl

- Stand on the ends of the elastic with both feet
- Grasp elastic in hands, palms up, arms straight
- Pull upward, bending at elbows, keeping trunk straight
- Slowly return to start position and repeat

Elbow Extension

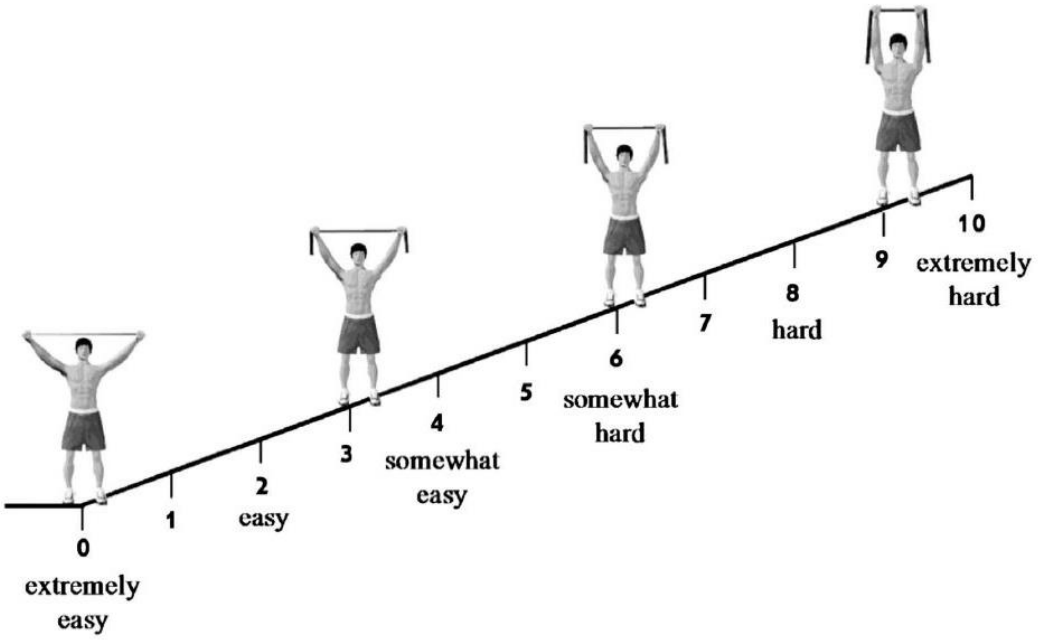


- Attach elastic to secure object using the door anchor at waist level
- Grasp elastic, thumb up, elbow bent, as shown
- Straighten elbow, keeping elbow at side.
- Slowly return to starting position

Elbow Kick Back

- Hold elastic in hand of involved arm
- Place one end of elastic under opposite foot.
- Slightly bend hips and support upper body with other arm as shown
- Pull up on elastic, raising elbow to shoulder height
- Extend elbow backward, contracting Triceps
- Slowly return to start position and repeat

Appendix 3c. *OMNI-RES RPE Scale (Colado et al., 2018)*



Appendix 4a. *Elements of the Senior Fitness Test used in the Trial*

30-Second Chair Stand

Purpose
To assess lower body strength, needed for numerous tasks such as climbing stairs, walking and getting out of a chair, tub or car. Also reduces the chance of falling.

Description
Number of full stands that can be completed in 30 seconds with arms folded across chest.

Risk zone
Less than 8 unassisted stands for men and women.

Arm Curl

Purpose
To assess upper body strength, needed for performing household and other activities involving lifting and carrying things such as groceries, suitcases and grandchildren.

Description
Number of bicep curls that can be completed in 30 seconds holding a hand weight of 5 lbs (2.27 kg) for women; 8 lbs (3.63 kg) for men.

Risk zone
Less than 11 curls using correct form for men and women.

Appendix 4b. *Questionnaire Booklet*

Questionnaire Booklet

Subject ID: _____

Testing session: _____

Included in this booklet are two quality of life questionnaires; one general (EQ-5D-5L) and one specific to prostate cancer (FACT-P). There is also an exercise questionnaire (Godin Leisure Time) and a tiredness or fatigue questionnaire (Brief Fatigue Inventory).

Please note, you do not have to answer any questions that make you feel upset or uncomfortable.

EQ-5D-5L – Quality of Life

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

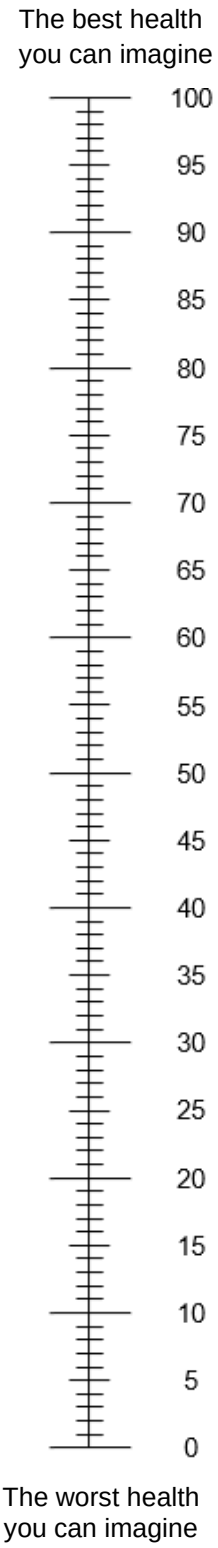
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

EQ-5D-5L VAS – Quality of Life

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



FACT-P (Version 4) – Quality of Life

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

PHYSICAL WELL-BEING

		Not at all	A little bit	Somewhat	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Somewhat	Quite a bit	Very much
GP1	I feel close to my friends	0	1	2	3	4
GP2	I get emotional support from my family	0	1	2	3	4
GP3	I get support from my friends	0	1	2	3	4
GP4	My family has accepted my illness	0	1	2	3	4
GP5	I am satisfied with family communication about my illness	0	1	2	3	4
GP6	I feel close to my partner (or the person who is my main support	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.* ☐					
GP7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4) – Quality of Life

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

<u>EMOTIONAL WELL-BEING</u>

		Not at all	A little bit	Somewhat	Quite a bit	Very much
GP1	I feel sad	0	1	2	3	4
GP2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GP3	I am losing hope in the fight against my illness	0	1	2	3	4
GP4	I feel nervous	0	1	2	3	4
GP5	I worry about dying	0	1	2	3	4
GP6	I worry that my condition will get worse	0	1	2	3	4

<u>FUNCTIONAL WELL-BEING</u>

		Not at all	A little bit	Somewhat	Quite a bit	Very much
GP1	I am able to work (include work at home)	0	1	2	3	4
GP2	My work (include work at home) is fulfilling	0	1	2	3	4
GP3	I am able to enjoy life	0	1	2	3	4
GP4	I have accepted my illness	0	1	2	3	4
GP5	I am sleeping well	0	1	2	3	4
GP6	I am enjoying the things I usually do for fun	0	1	2	3	4
GP7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4) – Quality of Life

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

<u>ADDITIONAL CONCERNS</u>

		Not at all	A little bit	Somewhat	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Godin Leisure Time Exercise Questionnaire (Modified)

For this question, we would like you to recall your average weekly exercise during the past month. We will ask you separate questions about aerobic or endurance exercise (i.e., exercise that improves the heart and lungs such as walking or swimming) and strength or resistance exercise (i.e. exercise that improves muscular strength such as weight lifting).

When answering these questions please remember:

- Only count exercise sessions that lasted 10 minutes or longer in duration.
- Only count exercise that was done during free time (i.e. not work or chores).
- Note that the main difference between the categories ‘a,’ ‘b’, and ‘c’ is the intensity of the aerobic (endurance) exercise and category ‘d’ is for strength (resistance) exercise.
- Please write the average frequency on the first line and the average duration on the second.
- If you did not do any exercise in one of the categories, please write in “0”.

Considering a typical week (7 days) over the <u>PAST MONTH</u> how many days on average did you do the following kinds of aerobic and strength exercise and what was the average duration?

	Average Frequency (days per week)	**Average Duration (minutes per session)**
VIGOROUS INTENSITY AEROBIC EXERCISE (HEART BEATS RAPIDLY, SWEATING) (e.g. running, aerobics classes, vigorous swimming, vigorous cycling).	_____	_____
MODERATE INTENSITY AEROBIC EXERCISE (NOT EXHAUSTING, LIGHT PERSPIRATION) (e.g. fast walking, tennis, easy bicycling, easy swimming, dancing).	_____	_____
LIGHT INTENSITY AEROBIC EXERCISE (MINIMAL EFFORT, NO PERSPIRATION) (e.g. easy walking, yoga, bowling, lawn bowling).	_____	_____
STRENGTH/RESISTANCE EXERCISE (MODERATE TO INTENSE EFFORT) (e.g. weight lifting, resistance bands, sit-ups, push-ups)	_____	_____

Brief Fatigue Inventory

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal work (includes both work outside the home and daily chores)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Appendix 4c. *Missing Data*

Outcome	Baseline		3 Month Follow-up		6 Month Follow-up	
	RET	**UC**	**RET**	**UC**	**RET**	**UC**
Flow Mediated Dilatation						
Baseline Diameter (mm)	6 (14.3%)	11 (26.2%)	12 (28.6%)	13 (31.0%)	10 (23.8%)	13 (31.0%)
Max Diameter (mm)	6 (14.3%)	11 (26.2%)	12 (28.6%)	13 (31.0%)	10 (23.8%)	13 (31.0%)
Recovery Diameter (mm)	6 (14.3%)	12 (28.6%)	12 (28.6%)	13 (31.0%)	10 (23.8%)	13 (31.0%)
FMD (%)	6 (14.3%)	11 (26.2%)	12 (28.6%)	13 (31.0%)	10 (23.8%)	13 (31.0%)
FMDr (%)	7 (16.7%)	12 (28.6%)	12 (28.6%)	13 (31.0%)	10 (23.8%)	13 (31.0%)
Shear Baseline (s^{-1})	9 (21.4%)	11 (26.2%)	12 (28.6%)	13 (31.0%)	10 (23.8%)	13 (31.0%)
Shear Max (s^{-1})	10 (23.8%)	11 (26.2%)	12 (28.6%)	13 (31.0%)	10 (23.8%)	13 (31.0%)
Shear Area	10 (23.8%)	11 (26.2%)	12 (28.6%)	13 (31.0%)	10 (23.8%)	13 (31.0%)
Shear Area to Max	10 (23.8%)	12 (28.6%)	12 (28.6%)	15 (35.7%)	10 (23.8%)	13 (31.0%)
Blood Biomarkers						
Glucose (mmol/L)	3 (7.1%)	1 (2.4%)	4 (9.5%)	7 (16.7%)	3 (7.1%)	4 (9.5%)
Insulin (µU/ml)	6 (14.3%)	2 (4.8%)	4 (9.5%)	9 (21.4%)	5 (11.9%)	8 (19.0%)
HOMA-IR	6 (14.3%)	2 (4.8%)	6 (14.3%)	9 (21.4%)	6 (14.3%)	8 (19.0%)
Total Chol (mmol/L)	1 (2.4%)	2 (4.8%)	3 (7.1%)	6 (14.3%)	2 (4.8%)	3 (7.1%)
HDL Cholesterol (mmol/L)	1 (2.4%)	2 (4.8%)	3 (7.1%)	6 (14.3%)	2 (4.8%)	3 (7.1%)
LDL Chiolesterol (mmol/L)	6 (14.3%)	7 (16.7%)	7 (16.7%)	8 (19.0%)	7 (16.7%)	7 (16.7%)
Non-HDL (mmol/L)	4 (9.5%)	4 (9.5%)	3 (7.1%)	6 (14.3%)	2 (4.8%)	3 (7.1%)
Triglycerides (mmol/L)	1 (2.4%)	2 (4.8%)	3 (7.1%)	6 (14.3%)	3 (7.1%)	3 (7.1%)
Total:HDL (mmol/L)	1 (2.4%)	2 (4.8%)	3 (7.1%)	6 (14.3%)	2 (4.8%)	3 (7.1%)

Cardiovascular Health						
Resting Heart Rate (bpm)	0 (100%)	0 (100%)	2 (4.8%)	1 (2.4%)	2 (4.8%)	3 (7.1%)
Blood pressure (mmHg)	0 (100%)	0 (100%)	2 (4.8%)	1 (2.4%)	2 (4.8%)	3 (7.1%)
QRisk-2 Score (%)	0 (100%)	0 (100%)	2 (4.8%)	1 (2.4%)	2 (4.8%)	3 (7.1%)
Anthropometric Profile						
Body Mass (kg)	0 (100%)	0 (100%)	2 (4.8%)	1 (2.4%)	2 (4.8%)	3 (7.1%)
BMI (kg/m^2)	0 (100%)	0 (100%)	2 (4.8%)	1 (2.4%)	2 (4.8%)	3 (7.1%)
Waist Circumference (cm)	0 (100%)	3 (7.1%)	2 (4.8%)	2 (4.8%)	2 (4.8%)	3 (7.1%)
Waist:Hip	0 (100%)	3 (7.1%)	2 (4.8%)	2 (4.8%)	2 (4.8%)	3 (7.1%)
Skinfolds	0 (100%)	3 (7.1%)	2 (4.8%)	2 (4.8%)	2 (4.8%)	3 (7.1%)
Submaximal Aerobic Exercise						
Stage	0 (100%)	0 (100%)	2 (4.8%)	1 (2.4%)	4 (9.5%)	3 (7.1%)
Time (secs)	0 (100%)	0 (100%)	2 (4.8%)	1 (2.4%)	4 (9.5%)	3 (7.1%)
Estimated $\dot{V}O_2$Peak (ml/kg/min)	0 (100%)	0 (100%)	2 (4.8%)	1 (2.4%)	4 (9.5%)	3 (7.1%)
Estimated METs	0 (100%)	0 (100%)	2 (4.8%)	1 (2.4%)	4 (9.5%)	3 (7.1%)
Max HR (bpm)	0 (100%)	0 (100%)	2 (4.8%)	1 (2.4%)	4 (9.5%)	3 (7.1%)
Strength						
Upper Body (reps)	0 (100%)	0 (100%)	2 (4.8%)	1 (2.4%)	2 (4.8%)	3 (7.1%)
Lower Body (reps)	0 (100%)	0 (100%)	2 (4.8%)	1 (2.4%)	2 (4.8%)	3 (7.1%)
Questionnaires						
EQ-5D	0 (100%)	0 (100%)	1 (2.4%)	3 (7.1%)	2 (4.8%)	4 (9.5%)
FACT-P	0 (100%)	0 (100%)	1 (2.4%)	3 (7.1%)	2 (4.8%)	4 (9.5%)
BFI	0 (100%)	0 (100%)	1 (2.4%)	3 (7.1%)	2 (4.8%)	4 (9.5%)
Godin Leisure Time Exercise Questionnaire (modified)	0 (100%)	0 (100%)	1 (2.4%)	3 (7.1%)	3 (7.1%)	4 (9.5%)

CHAPTER 9

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9.0 References

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